**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder contains 50 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| **Body weight (kg)** | **PegIntron** | | **Ribavirin capsules** | |
|---|---|---|---|---|
| | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Total daily dose (mg)** | **Number of capsules (200 mg)** |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7 [d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

**4.3 Contraindications**

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment | Sustained Virologic Response | Relapse |

| | response | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table 11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used

immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder is contained in a 2 ml vial (Type I flint glass) with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule (Type I flint glass). PegIntron 50 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is to be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 50 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. Any unused material is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/001
EU/1/00/131/002
EU/1/00/131/003

EU/1/00/131/004
EU/1/00/131/005
EU/1/00/131/026

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency
http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder contains 80 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| **Body weight (kg)** | **PegIntron** | | **Ribavirin capsules** | |
|---|---|---|---|---|
| | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Total daily dose (mg)** | **Number of capsules (200 mg)** |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7 [d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicinesmetabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment | Sustained Virologic Response | Relapse |

| | response | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used

immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder is contained in a 2 ml vial (Type I flint glass) with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule (Type I flint glass). PegIntron 80 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is to be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. Any unused material is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/006
EU/1/00/131/007
EU/1/00/131/008

EU/1/00/131/009
EU/1/00/131/010
EU/1/00/131/027

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder contains 100 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment | Sustained Virologic Response | Relapse |

| | response | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used

immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder is contained in a 2 ml vial (Type I flint glass) with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule (Type I flint glass). PegIntron 100 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is to be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 100 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. Any unused material is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/011
EU/1/00/131/012
EU/1/00/131/013

EU/1/00/131/014
EU/1/00/131/015
EU/1/00/131/028

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder contains 120 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment | Sustained Virologic Response | Relapse |

| | response | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used

immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder is contained in a 2 ml vial (Type I flint glass) with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule (Type I flint glass). PegIntron 120 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is to be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 120 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. Any unused material is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/016
EU/1/00/131/017
EU/1/00/131/018

EU/1/00/131/019
EU/1/00/131/020
EU/1/00/131/029

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of PegIntron, powder contains 150 micrograms of peginterferon alfa-2b as measured on a protein basis.
Each vial provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 μg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment | Sustained Virologic Response | Relapse |

| | response | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | n = 107 | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used

immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder is contained in a 2 ml vial (Type I flint glass) with a butyl rubber stopper in an aluminium flip-off seal with a polypropylene bonnet. The solvent is presented in a 2 ml ampoule (Type I flint glass). PegIntron 150 micrograms is supplied as:

- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use.
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Each vial is to be reconstituted with 0.7 ml of water for injections for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 150 micrograms/0.5 ml.

Using a sterilised injection syringe and injection needle, 0.7 ml of water for injections is injected into the vial of PegIntron. Dissolution of powder is completed by agitating it gently. The appropriate dose can then be withdrawn with a sterilised injection syringe and injected. A complete set of instructions is provided in the Annex to the Package Leaflet.

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. Any unused material is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/021
EU/1/00/131/022
EU/1/00/131/023

EU/1/00/131/024
EU/1/00/131/025
EU/1/00/131/030

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms, powder and solvent for solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 50 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder , and the corresponding amount of solvent, to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below "Laboratory tests" and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 µg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment response | Sustained Virologic Response | Relapse |

| | | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory
*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

Deliverable volume from pen = 0.5 ml.

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 50 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 50 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded.

**7. MARKETING AUTHORISATION HOLDER**

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/031
EU/1/00/131/032
EU/1/00/131/033
EU/1/00/131/034

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms, powder and solvent for solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 80 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder , and the corresponding amount of solvent, to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % Cl for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 µg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment response | Sustained Virologic Response | Relapse |

| | | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/m$^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

Deliverable volume from pen = 0.5 ml.

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 80 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 80 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded.

**7. MARKETING AUTHORISATION HOLDER**

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/035
EU/1/00/131/036
EU/1/00/131/037
EU/1/00/131/038

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms, powder and solvent for solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 100 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder , and the corresponding amount of solvent, to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % Cl for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 µg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment response | Sustained Virologic Response | Relapse |

| | | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/$m^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

Deliverable volume from pen = 0.5 ml.

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 100 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 100 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded.

**7. MARKETING AUTHORISATION HOLDER**

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/039
EU/1/00/131/040
EU/1/00/131/041
EU/1/00/131/042

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms, powder and solvent for solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 120 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder , and the corresponding amount of solvent, to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7 [d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 µg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment response | Sustained Virologic Response | Relapse |

| | | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/$m^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

Deliverable volume from pen = 0.5 ml.

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

### 6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

### 6.5 Nature and contents of container

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 120 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal

Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 120 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, the reconstituted solution is to be inspected visually prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded.

## 7. MARKETING AUTHORISATION HOLDER

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/043
EU/1/00/131/044
EU/1/00/131/045
EU/1/00/131/046

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms, powder and solvent for solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen of PegIntron 150 micrograms contains a sufficient amount of peginterferon alfa-2b as measured on a protein basis in a powder , and the corresponding amount of solvent, to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

The active substance is a covalent conjugate of recombinant interferon alfa-2b* with monomethoxy polyethylene glycol. The potency of this product should not be compared to that of another pegylated or nonpegylated protein of the same therapeutic class (see section 5.1).
*produced by rDNA technology in *E.coli* cells harbouring a genetically engineered plasmid hybrid encompassing an interferon alfa-2b gene from human leukocytes

*Excipients:*
PegIntron contains 40 mg of sucrose per 0.5 ml.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection in pre-filled pen.

White powder.
Clear and colourless solvent.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

*Adult patients:*
PegIntron is indicated for the treatment of adult patients with chronic hepatitis C who are positive for hepatitis C virus RNA (HCV-RNA), including patients with compensated cirrhosis and/or co-infected with clinically stable HIV (see section 4.4).

The best way to use PegIntron in this indication is in combination with ribavirin.

This combination is indicated in naïve patients including patients with clinically stable HIV co-infection and in patients who have failed previous treatment with interferon alpha (pegylated or nonpegylated) and ribavirin combination therapy or interferon alpha monotherapy (see section 5.1).

Interferon monotherapy, including PegIntron, is indicated mainly in case of intolerance or contraindication to ribavirin.

*Paediatric patients 3 years of age and older:*
PegIntron is indicated in a combination regimen with ribavirin for the treatment of children 3 years of age and older and adolescents, who have chronic hepatitis C, not previously treated, without liver decompensation, and who are positive for HCV-RNA.

When deciding not to defer treatment until adulthood, it is important to consider that the combination therapy induced a growth inhibition. The reversibility of growth inhibition is uncertain. The decision to treat should be made on a case by case basis (see section 4.4).

Please refer also to the ribavirin Summary of Product Characteristics (SPC) for capsules or oral solution when PegIntron is to be used in combination with ribavirin.

## 4.2 Posology and method of administration

Treatment should be initiated and monitored only by a physician experienced in the management of patients with hepatitis C.

- Dose to be administered

PegIntron should be administered as a once weekly subcutaneous injection. The dose administered in adults depends on whether it is used in combination with ribavirin or as monotherapy.

PegIntron and ribavirin combination therapy

- Adult patients:

PegIntron 1.5 micrograms/kg/week in combination with ribavirin capsules.

The intended dose of 1.5 μg/kg of PegIntron to be used in combination with ribavirin may be delivered in weight categories with the pen/vial strengths according to **Table 1**. Ribavirin capsules are to be administered orally each day in two divided doses with food (morning and evening).

**Table 1 Dosing for combination therapy**

| Body weight (kg) | PegIntron | | Ribavirin capsules | |
|---|---|---|---|---|
| | Vial/Pen strength (μg/0.5ml) | Administer once weekly (ml) | Total daily dose (mg) | Number of capsules (200 mg) |
| < 40 | 50 | 0.5 | 800 | 4[a] |
| 40-50 | 80 | 0.4 | 800 | 4[a] |
| 51-64 | 80 | 0.5 | 800 | 4[a] |
| 65-75 | 100 | 0.5 | 1,000 | 5[b] |
| 76-80 | 120 | 0.5 | 1,000 | 5[b] |
| 81-85 | 120 | 0.5 | 1,200 | 6[c] |
| 86-105 | 150 | 0.5 | 1,200 | 6[c] |
| > 105 | 150 | 0.5 | 1,400 | 7[d] |

a: 2 morning, 2 evening
b: 2 morning, 3 evening
c: 3 morning, 3 evening
d: 3 morning, 4 evening

*Duration of treatment – Naïve patients*
*Predictability of sustained virological response:* Patients infected with virus genotype 1 who fail to achieve undetectable HCV-RNA or demonstrate adequate virological response at week 4 or 12 are highly unlikely to become sustained virological responders and should be evaluated for discontinuation (see also section 5.1).

- Genotype 1:
  - Patients who have undetectable HCV-RNA at treatment week 12, treatment should be continued for another nine month period (i.e., a total of 48 weeks).
  - Patients with detectable but ≥ 2 log decrease in HCV-RNA level from baseline at treatment week 12 should be reassessed at treatment week 24 and, if HCV-RNA is undetectable, they

should continue with full course of therapy (i.e. a total of 48 weeks). However, if HCV-RNA is still detectable at treatment week 24, discontinuation of therapy should be considered.
- In the subset of patients with genotype 1 infection and low viral load (< 600,000 IU/ml) who become HCV-RNA negative at treatment week 4 and remain HCV-RNA negative at week 24, the treatment could either be stopped after this 24 week treatment course or pursued for an additional 24 weeks (i.e. overall 48 weeks treatment duration). However, an overall 24 weeks treatment duration may be associated with a higher risk of relapse than a 48 weeks treatment duration (see section 5.1).

- Genotypes 2 or 3:
  It is recommended that all patients be treated for 24 weeks, except for HCV/HIV co-infected patients who should receive 48 weeks of treatment.
- Genotype 4:
  In general, patients infected with genotype 4 are considered harder to treat and limited study data (n=66) indicate they are compatible with a duration of treatment as for genotype 1.

*Duration of treatment - HCV/HIV co-infection*
The recommended duration of treatment for HCV/HIV co-infected patients is 48 weeks, regardless of genotype.
*Predictability of response and non-response in HCV/HIV co-infection*
Early virological response by week 12, defined as a 2 log viral load decrease or undetectable levels of HCV-RNA, has been shown to be predictive for sustained response. The negative predictive value for sustained response in HCV/HIV co-infected patients treated with PegIntron in combination with ribavirin was 99 % (67/68; Study 1) (see section 5.1). A positive predictive value of 50 % (52/104; Study 1) was observed for HCV/HIV co-infected patients receiving combination therapy.

*Duration of treatment - Retreatment*
*Predictability of sustained virological response*: All patients, irrespective of genotype, who have demonstrated serum HCV-RNA below the limits of detection at week 12 should receive 48 weeks of therapy. Retreated patients who fail to achieve virological response (i.e. HCV-RNA below the limits of detection) at week 12 are unlikely to become sustained virological responders after 48 weeks of therapy (see also section 5.1).
Retreatment duration greater than 48 weeks in non-responder patients with genotype 1 has not been studied with pegylated interferon alfa-2b and ribavirin combination therapy.

- Paediatric patients 3 years of age and older :

Dosing for children and adolescent patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 $\mu g/m^2$/week subcutaneously in combination with ribavirin 15 mg/kg/day orally in two divided doses with food (morning and evening).

*Duration of treatment*
- Genotype 1:
  The recommended duration of treatment is 1 year. By extrapolation from clinical data on combination therapy with standard interferon in paediatric patients (negative predictive value 96 % for interferon alfa–2b/ribavirin), patients who fail to achieve virological response at 12 weeks are highly unlikely to become sustained virological responders. Therefore, it is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.
- Genotype 2 or 3:
  The recommended duration of treatment is 24 weeks.
- Genotype 4:
  Only 5 children and adolescents with Genotype 4 were treated in the PegIntron/ribavirin clinical trial. The recommended duration of treatment is 1 year. It is recommended that children and adolescent patients receiving PegIntron/ribavirin combination be discontinued from therapy if

their week 12 HCV-RNA dropped < 2 $\log_{10}$ compared to pretreatment or if they have detectable HCV-RNA at treatment week 24.

PegIntron monotherapy – Adults

As monotherapy the PegIntron regimen is 0.5 or 1.0 μg/kg/week. The lowest vial or pen strength available is 50 μg/0.5 ml; therefore for patients prescribed 0.5 μg/kg/week, doses must be adjusted by volume as shown in **Table 2**. For the 1.0 μg/kg dose, similar volume adjustments can be made or alternate vial strengths can be used as shown in **Table 2**. PegIntron monotherapy was not studied in HCV/HIV co-infected patients.

**Table 2 Monotherapy dosing**

| | **0.5 μg/kg** | | **1.0 μg/kg** | |
|---|---|---|---|---|
| **Body weight (kg)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** | **Vial/Pen strength (μg/0.5ml)** | **Administer once weekly (ml)** |
| 30-35 | 50* | 0.15 | 50 | 0.3 |
| 36-45 | 50* | 0.2 | 50 | 0.4 |
| 46-56 | 50* | 0.25 | 50 | 0.5 |
| 57-72 | 50 | 0.3 | 80 | 0.4 |
| 73-88 | 50 | 0.4 | 80 | 0.5 |
| 89-106 | 50 | 0.5 | 100 | 0.5 |
| 106-120** | 80 | 0.4 | 120 | 0.5 |

* Must use vial. Minimum delivery for pen is 0.3 ml.
** For patients > 120 kg, the PegIntron dose should be calculated based on the individual patient weight.

*Duration of treatment*

For patients who exhibit virological response at week 12, treatment should be continued for at least another three-month period (i.e., a total of six months). The decision to extend therapy to one year of treatment should be based on prognostic factors (e.g., genotype, age > 40 years, male gender, bridging fibrosis).

- Dose modification for all patients

If severe adverse reactions or laboratory abnormalities develop during treatment with PegIntron monotherapy or PegIntron in combination with ribavirin, modify the dosages of each product as appropriate, until the adverse reactions abate. As adherence might be of importance for outcome of therapy, the dose should be kept as close as possible to the recommended standard dose. Guidelines were developed in clinical trials for dose modification.

Combination therapy dose reduction guidelines

**Table 2a Dose modification guidelines for combination therapy (with ribavirin) based on laboratory parameters**

| **Laboratory values** | **Reduce only ribavirin daily dose (see note 1) if:** | **Reduce only PegIntron dose (see note 2) if:** | **Discontinue combination therapy if:** |
|---|---|---|---|
| Haemoglobin | < 10 g/dl | - | < 8.5 g/dl |
| Adults:Haemoglobin in: Patients with history of stable cardiac disease Children and | ≥ 2 g/dl decrease in haemoglobin during any four week period during treatment (permanent dose reduction) | | < 12 g/dl after four weeks of dose reduction |

| | | | |
|---|---|---|---|
| adolescents: not applicable | | | |
| Leukocytes | - | < 1.5 x $10^9$/l | < 1.0 x $10^9$/l |
| Neutrophils | - | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | - | < 50 x $10^9$/l (adults)<br><70 x $10^9$/l (children and adolescents) | < 25 x $10^9$/l (adults)<br>< 50 x $10^9$/l (children and adolescents) |
| Bilirubin – direct | - | - | 2.5 x ULN* |
| Bilirubin - indirect | > 5 mg/dl | - | > 4 mg/dl (for > 4 weeks) |
| Serum Creatinine | - | - | > 2.0 mg/dl |
| Creatinine Clearance | - | - | Discontinue ribavirin if CrCL < 50ml/min |
| Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) | - | - | 2 x baseline and > 10 x ULN*<br><br>2 x baseline and > 10 x ULN* |

* Upper limit of normal

Note 1: In adult patients 1st dose reduction of ribavirin is by 200 mg/day (except in patients receiving the 1,400 mg, dose reduction should be by 400 mg/day). If needed, 2nd dose reduction of ribavirin is by an additional 200 mg/day. Patients whose dose of ribavirin is reduced to 600 mg daily receive one 200 mg capsule in the morning and two 200 mg capsules in the evening.
In children and adolescent patients 1st dose reduction of ribavirin is to 12 mg/kg/day, 2nd dose reduction of ribavirin is to 8 mg/kg/day.

Note 2: In adult patients 1st dose reduction of PegIntron is to 1 μg/kg/week. If needed, 2nd dose reduction of PegIntron is to 0.5 μg/kg/week. For patients on PegIntron monotherapy: refer to monotherapy dose reduction guidelines section for dose reduction.
In children and adolescent patients 1st dose reduction of PegIntron is to 40 μg/$m^2$/week, 2nd dose reduction of PegIntron is to 20 μg/$m^2$/week.

Dose reduction of PegIntron in adults may be accomplished by reducing the prescribed volume or by utilizing a lower dose strength as shown in **Table 2b**. Dose reduction of PegIntron in children and adolescents is accomplished by modifying the recommended dose in a two-step process from the original starting dose of 60 μg/$m^2$/week, to 40 μg/$m^2$/week, then to 20 μg/$m^2$/week, if needed.

| Table 2b Two-step dose reduction of PegIntron in combination therapy in adults | | | | | | | |
|---|---|---|---|---|---|---|---|
| **First dose reduction to PegIntron 1 µg/kg** | | | | **Second dose reduction to PegIntron 0.5 µg/kg** | | | |
| **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** | **Body weight kg** | **PegIntron strength to use** | **Amount of PegIntron (µg) to administer** | **Volume (ml) of PegIntron to administer** |
| < 40 | 50 µg per 0.5 ml | 35 | 0.35 | < 40 | 50 µg per 0.5 ml* | 20 | 0.2 |
| 40 – 50 | | 45 | 0.45 | 40 – 50 | | 25 | 0.25 |
| 51 – 64 | 80 µg per 0.5 ml | 56 | 0.35 | 51 – 64 | 50 µg per 0.5 ml | 30 | 0.3 |
| 65 – 75 | | 72 | 0.45 | 65 – 75 | | 35 | 0.35 |
| 76 – 85 | | 80 | 0.5 | 76 – 85 | | 45 | 0.45 |
| 86 - 105 | 120 µg per 0.5 ml | 96 | 0.4 | 86 – 105 | | 50 | 0.5 |
| > 105 | | 108 | 0.45 | > 105 | 80 µg per 0.5 ml | 64 | 0.4 |

* Must use vial. Minimum delivery for pen 0.3 ml

PegIntron monotherapy dose reduction guidelines in adults

Dose modification guidelines for adult patients who use PegIntron monotherapy are shown in **Table 3a.**

| Table 3a Dose modification guidelines for PegIntron monotherapy in adults based on laboratory parameters | | |
|---|---|---|
| **Laboratory values** | **Reduce PegIntron to one-half dose if:** | **Discontinue PegIntron if:** |
| Neutrophils | < 0.75 x $10^9$/l | < 0.5 x $10^9$/l |
| Platelets | < 50 x $10^9$/l | < 25 x $10^9$/l |

Dose reduction for adult patients who use 0.5 µg/kg PegIntron monotherapy must be accomplished by reducing the prescribed volume by one-half. The 50 µg/0.5 ml vial must be used if necessary since the pen can only deliver a minimum volume of 0.3 ml.

For adult patients who use 1.0 µg/kg PegIntron monotherapy, dose reduction may be accomplished by reducing the prescribed volume by one-half or by utilizing a lower dose strength as shown in **Table 3b**.

| Table 3b Reduced PegIntron dose for the 1.0 µg/kg monotherapy regimen in adults | | | | |
|---|---|---|---|---|
| **Body weight (kg)** | **Target reduced dose (µg)** | **Vial/Pen strength (µg/0.5ml)** | **Administer once weekly (ml)** | **Amount delivered (µg)** |
| 30-35 | 15 | 50* | 0.15 | 15 |
| 36-45 | 20 | 50* | 0.20 | 20 |
| 46-56 | 25 | 50* | 0.25 | 25 |

| | | | | |
|---|---|---|---|---|
| 57-72 | 32 | 50 | 0.3 | 30 |
| 73-89 | 40 | 50 | 0.4 | 40 |
| 90-106 | 50 | 50 | 0.5 | 50 |
| > 106 | 60 | 80 | 0.4 | 64 |
| *Must use vial. Minimum delivery for pen is 0.3 ml. | | | | |

- Special populations

Use in renal impairment:
*Monotherapy*:
PegIntron should be used with caution in patients with moderate to severe renal impairment. In patients with moderate renal dysfunction (creatinine clearance 30-50 ml/minute), the starting dose of PegIntron should be reduced by 25 %. Patients with severe renal dysfunction (creatinine clearance 15-29 ml/minute) should have the starting dose of PegIntron reduced by 50 %. Data are not available for the use of PegIntron in patients with creatinine clearance < 15 ml/minute (see section 5.2). Patients with severe renal impairment, including those on hemodialysis, should be closely monitored. If renal function decreases during treatment, PegIntron therapy should be discontinued.

*Combination therapy*:
Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see ribavirin SPC). When administered in combination with ribavirin**,** subjects with impaired renal function should be more carefully monitored with respect to the development of anaemia.

Use in hepatic impairment:
The safety and efficacy of PegIntron therapy has not been evaluated in patients with severe hepatic dysfunction, therefore PegIntron must not be used for these patients.

Use in the elderly (≥ 65 years of age):
There are no apparent age-related effects on the pharmacokinetics of PegIntron. Data from elderly patients treated with a single dose of PegIntron suggest no alteration in PegIntron dose is necessary based on age (see section 5.2).

Use in paediatric patients:
PegIntron can be used in combination with ribavirin in paediatric patients 3 years of age and older.

## 4.3 Contraindications

- Hypersensitivity to the active substance or to any interferon or to any of the excipients;
- A history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous six months (see section 4.4);
- Severe, debilitating medical conditions;
- Autoimmune hepatitis or a history of autoimmune disease;
- Severe hepatic dysfunction or decompensated cirrhosis of the liver;
- Pre-existing thyroid disease unless it can be controlled with conventional treatment;
- Epilepsy and/or compromised central nervous system (CNS) function;
- HCV/HIV patients with cirrhosis and a Child-Pugh score ≥ 6.

Paediatric patients:
- Existence of, or history of severe psychiatric condition, particularly severe depression, suicidal ideation or suicidal attempt.

*Combination therapy with ribavirin*: Also see ribavirin Summary of the Product Characteristics (SPC) if PegIntron is to be administered in combination with ribavirin in patients with chronic hepatitis C.

## 4.4 Special warnings and precautions for use

**Psychiatric and Central Nervous System (CNS)**:
Severe CNS effects, particularly depression, suicidal ideation and attempted suicide have been observed in some patients during PegIntron therapy, and even after treatment discontinuation mainly during the 6-month follow-up period. Other CNS effects including aggressive behaviour (sometimes directed against others such as homicidal ideation), bipolar disorders, mania, confusion and alterations of mental status have been observed with alpha interferons. Patients should be closely monitored for any signs or symptoms of psychiatric disorders. If such symptoms appear, the potential seriousness of these undesirable effects must be borne in mind by the prescribing physician and the need for adequate therapeutic management should be considered. If psychiatric symptoms persist or worsen, or suicidal ideation is identified, it is recommended that treatment with PegIntron be discontinued, and the patient followed, with psychiatric intervention as appropriate.

*Patients with existence of, or history of severe psychiatric conditions:* If treatment with peginterferon alfa-2b is judged necessary in patients with existence or history of severe psychiatric conditions, this should only be initiated after having ensured appropriate individualised diagnostic and therapeutic management of the psychiatric condition.
- The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see section 4.3). Among children and adolescents treated with interferon alfa-2b in combination with ribavirin, suicidal ideation or attempts were reported more frequently compared to adult patients (2.4 % vs 1 %) during treatment and during the 6-month follow-up after treatment. As in adult patients, children and adolescents experienced other psychiatric adverse events (e.g. depression, emotional lability, and somnolence).

**Growth and development (children and adolescents):**
During the course of therapy lasting up to 48 weeks in patients ages 3 through 17 years, weight loss and growth inhibition were common (see sections 4.8 and 5.1). The longer term data available in children treated with the combination therapy with standard interferon/ribavirin are also indicative of substantial growth retardation (> 15 percentile decrease in height percentile as compared to baseline) in 21 % of children despite being off treatment for more than 5 years.

*Case by case benefit/risk assessment in children:*
The expected benefit of treatment should be carefully weighed against the safety findings observed for children and adolescents in the clinical trials (see sections 4.8 and 5.1).
- It is important to consider that the combination therapy induced a growth inhibition, the reversibility of which is uncertain.
- This risk should be weighed against the disease characteristics of the child, such as evidence of disease progression (notably fibrosis), co-morbidities that may negatively influence the disease progression (such as HIV co-infection), as well as prognostic factors of response (HCV genotype and viral load).

Whenever possible the child should be treated after the pubertal growth spurt, in order to reduce the risk of growth inhibition. There are no data on long term effects on sexual maturation.

More significant obtundation and coma, including cases of encephalopathy, have been observed in some patients, usually elderly, treated at higher doses for oncology indications. While these effects are generally reversible, in a few patients full resolution took up to three weeks. Very rarely, seizures have occurred with high doses of interferon alpha.

All patients in the selected chronic hepatitis C studies had a liver biopsy before inclusion, but in certain cases (i.e. patients with genotype 2 and 3), treatment may be possible without histological confirmation. Current treatment guidelines should be consulted as to whether a liver biopsy is needed prior to commencing treatment.

Acute hypersensitivity: Acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis) have been observed rarely during interferon alfa-2b therapy. If such a

reaction develops during treatment with PegIntron, discontinue treatment and institute appropriate medical therapy immediately. Transient rashes do not necessitate interruption of treatment.

Cardiovascular system: As with interferon alfa-2b, adult patients with a history of congestive heart failure, myocardial infarction and/or previous or current arrhythmic disorders, receiving PegIntron therapy require close monitoring. It is recommended that patients who have pre-existing cardiac abnormalities have electrocardiograms taken prior to and during the course of treatment. Cardiac arrhythmias (primarily supraventricular) usually respond to conventional therapy but may require discontinuation of PegIntron therapy. There are no data in children or adolescents with a history of cardiac disease.

Liver function: As with all interferons, discontinue treatment with PegIntron in patients who develop prolongation of coagulation markers which might indicate liver decompensation.

Pyrexia: While pyrexia may be associated with the flu-like syndrome reported commonly during interferon therapy, other causes of persistent pyrexia must be ruled out.

Hydration: Adequate hydration must be maintained in patients undergoing PegIntron therapy since hypotension related to fluid depletion has been seen in some patients treated with alpha interferons. Fluid replacement may be necessary.

Pulmonary changes: Pulmonary infiltrates, pneumonitis, and pneumonia, occasionally resulting in fatality, have been observed rarely in interferon alpha treated patients. Any patient developing pyrexia, cough, dyspnea or other respiratory symptoms must have a chest X-ray taken. If the chest X-ray shows pulmonary infiltrates or there is evidence of pulmonary function impairment, the patient is to be monitored closely, and, if appropriate, discontinue interferon alpha. Prompt discontinuation of interferon alpha administration and treatment with corticosteroids appear to be associated with resolution of pulmonary adverse events.

Autoimmune disease: The development of auto-antibodies and autoimmune disorders has been reported during treatment with alpha interferons. Patients predisposed to the development of autoimmune disorders may be at increased risk. Patients with signs or symptoms compatible with autoimmune disorders should be evaluated carefully, and the benefit-risk of continued interferon therapy should be reassessed (see also section 4.4 Thyroid changes and section 4.8).
Cases of Vogt-Koyanagi-Harada (VKH) syndrome have been reported in patients with chronic hepatitis C treated with interferon. This syndrome is a granulomatous inflammatory disorder affecting the eyes, auditory system, meninges, and skin. If VKH syndrome is suspected, antiviral treatment should be withdrawn and corticosteroid therapy discussed (see section 4.8).

Ocular changes: Ophthalmologic disorders, including retinal haemorrhages, retinal exudates, and retinal artery or vein occlusion have been reported in rare instances after treatment with alpha interferons (see section 4.8). All patients should have a baseline eye examination. Any patient complaining of ocular symptoms, including loss of visual acuity or visual field must have a prompt and complete eye examination. Periodic visual examinations are recommended during PegIntron therapy, particularly in patients with disorders that may be associated with retinopathy, such as diabetes mellitus or hypertension. Discontinuation of PegIntron should be considered in patients who develop new or worsening ophthalmological disorders.

Thyroid changes: Infrequently, adult patients treated for chronic hepatitis C with interferon alpha have developed thyroid abnormalities, either hypothyroidism or hyperthyroidism. Approximately 21 % of children treated with PegIntron/ribavirin combination therapy developed increase in thyroid stimulating hormone (TSH). Another approximately 2 % had a transient decrease below the lower limit of normal. Prior to initiation of PegIntron therapy, TSH levels must be evaluated and any thyroid abnormality detected at that time must be treated with conventional therapy. Determine TSH levels if, during the course of therapy, a patient develops symptoms consistent with possible thyroid dysfunction. In the presence of thyroid dysfunction, PegIntron treatment may be continued if TSH levels can be maintained in the normal range by medicine. Children and adolescents should be monitored every 3 months for evidence of thyroid dysfunction (e.g. TSH).

Metabolic disturbances: Hypertriglyceridemia and aggravation of hypertriglyceridemia, sometimes severe, have been observed. Monitoring of lipid levels is, therefore, recommended.

HCV/HIV Co-infection

*Mitochondrial toxicity and lactic acidosis:*

Patients co-infected with HIV and receiving Highly Active Anti-Retroviral Therapy (HAART) may be at increased risk of developing lactic acidosis. Caution should be used when adding PegIntron and ribavirin to HAART therapy (see ribavirin SPC).

*Hepatic decompensation in HCV/HIV co-infected patients with advanced cirrhosis:*

Co-infected patients with advanced cirrhosis receiving HAART may be at increased risk of hepatic decompensation and death. Adding treatment with alfa interferons alone or in combination with ribavirin may increase the risk in this patient subset. Other baseline factors in co-infected patients that may be associated with a higher risk of hepatic decompensation include treatment with didanosine and elevated bilirubin serum concentration.

Co-infected patients receiving both antiretroviral (ARV) and anti-hepatitis treatment should be closely monitored, assessing their Child-Pugh score during treatment. Patients progressing to hepatic decompensation should have their anti-hepatitis treatment immediately discontinued and the ARV treatment reassessed.

*Haematological abnormalities in HCV/HIV co-infected patients:*

HCV/HIV co-infected patients receiving peginterferon alfa-2b/ribavirin treatment and HAART may be at increased risk to develop haematological abnormalities (as neutropenia, thrombocytopenia and anaemia) compared to HCV mono-infected patients. Although, the majority of them could be managed by dose reduction, close monitoring of haematological parameters should be undertaken in this population of patients (see section 4.2 and below “Laboratory tests” and section 4.8).

Patients treated with PegIntron and ribavirin combination therapy and zidovudine are at increased risk of developing anaemia and therefore the concomitant use of this combination with zidovudine is not recommended (see section 4.5).

*Patients with low CD4 counts:*

In patients co-infected with HCV/HIV, limited efficacy and safety data (N = 25) are available in subjects with CD4 counts less than 200 cells/µl. Caution is therefore warranted in the treatment of patients with low CD4 counts.

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron and ribavirin.

Dental and periodontal disorders: Dental and periodontal disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with the combination of PegIntron and ribavirin. Patients should brush their teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If this reaction occurs, they should be advised to rinse out their mouth thoroughly afterwards.

Organ transplant recipients: The safety and efficacy of PegIntron alone or in combination with ribavirin for the treatment of hepatitis C in liver or other organ transplant recipients have not been studied. Preliminary data indicate that interferon alpha therapy may be associated with an increased rate of kidney graft rejection. Liver graft rejection has also been reported.

Other: Due to reports of interferon alpha exacerbating pre-existing psoriatic disease and sarcoidosis, use of PegIntron in patients with psoriasis or sarcoidosis is recommended only if the potential benefit justifies the potential risk.

Laboratory tests: Standard haematologic tests, blood chemistry and a test of thyroid function must be conducted in all patients prior to initiating therapy. Acceptable baseline values that may be considered as a guideline prior to initiation of PegIntron therapy are:

- Platelets ≥ 100,000/$mm^3$
- Neutrophil count ≥ 1,500/$mm^3$
- TSH level must be within normal limits

Laboratory evaluations are to be conducted at weeks 2 and 4 of therapy, and periodically thereafter as clinically appropriate. HCV-RNA should be measured periodically during treatment (see section 4.2).

Important information about some of the ingredients of PegIntron:
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase-isomaltase insufficiency should not take this medicine.
This medicinal product contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 4.5 Interaction with other medicinal products and other forms of interaction

Results from a multiple-dose probe study assessing P450 substrates in chronic hepatitis C patients receiving once weekly PegIntron (1.5 µg/kg) for 4 weeks demonstrated an increase in activity of CYP2D6 and CYP2C8/9. No change in activity of CYP1A2, CYP3A4, or N-acetyltransferase was observed.

Caution should be used when administering peginterferon alfa-2b with medicines metabolised by CYP2D6 and CYP2C8/9, especially those with narrow therapeutic window, such as warfarin and phenytoin (CYP2C9) and flecainide (CYP2D6).

These findings may partly relate to improved metabolic capacity due to reduced hepatic inflammation in patients undergoing treatment with PegIntron. Caution is therefore advised when PegIntron treatment is initiated for chronic hepatitis in patients treated with medicine with a narrow therapeutic window and sensitive to mild metabolic impairment of the liver.

No pharmacokinetic interactions were noted between PegIntron and ribavirin in a multiple-dose pharmacokinetic study.

Methadone:
In patients with chronic hepatitis C that were on stable methadone maintenance therapy and naïve to peginterferon alfa-2b, addition of 1.5 microgram/kg/week of PegIntron subcutaneously for 4 weeks increased R-methadone AUC by approximately 15 % (95 % CI for AUC ratio estimate 103 – 128 %). The clinical significance of this finding is unknown; however, patients should be monitored for signs and symptoms of increased sedative effect, as well as respiratory depression. Especially in patients on a high dose of methadone, the risk for QTc prolongation should be considered.

HCV/HIV Co-infection:
Nucleoside analogs: Use of nucleoside analogs, alone or in combination with other nucleosides, has resulted in lactic acidosis. Pharmacologically, ribavirin increases phosphorylated metabolites of purine nucleosides *in vitro*. This activity could potentiate the risk of lactic acidosis induced by purine nucleoside analogs (e.g. didanosine or abacavir). Co-administration of ribavirin and didanosine is not recommended. Reports of mitochondrial toxicity, in particular lactic acidosis and pancreatitis, of which some fatal, have been reported (see ribavirin SPC).

Exacerbation of anaemia due to ribavirin has been reported when zidovudine is part of the regimen used to treat HIV, although the exact mechanism remains to be elucidated. The concomitant use of ribavirin with zidovudine is not recommended due to an increased risk of anaemia (see section 4.4). Consideration should be given to replacing zidovudine in a combination anti-retroviral treatment

(ART) regimen if this is already established. This would be particularly important in patients with a known history of zidovudine-induced anaemia.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in males and females
PegIntron is recommended for use in fertile women only when they are using effective contraception during the treatment.

*Combination therapy with ribavirin:*
Extreme care must be taken to avoid pregnancy in female patients or in partners of male patients taking PegIntron in combination with ribavirin. Females of childbearing potential and their partners must each use an effective contraceptive during treatment and for 4 months after treatment has been concluded. Male patients and their female partners must each use an effective contraceptive during treatment and for 7 months after treatment has been concluded (see ribavirin SPC).

Pregnancy
There are no adequate data from the use of interferon alfa-2b in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Interferon alfa-2b has been shown to be abortifacient in primates. PegIntron is likely to also cause this effect.
The potential risk in humans is unknown. PegIntron is to be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

*Combination therapy with ribavirin:*
Ribavirin causes serious birth defects when administered during pregnancy, therefore ribavirin therapy is contraindicated in women who are pregnant.

Breast-feeding
It is not known whether the components of this medicinal product are excreted in human milk. Because of the potential for adverse reactions in breast-fed infants, breast-feeding should be discontinued prior to initiation of treatment.

## 4.7 Effects on ability to drive and use machines

Patients who develop fatigue, somnolence or confusion during treatment with PegIntron are cautioned to avoid driving or operating machines.

## 4.8 Undesirable effects

*Adults*
The most common treatment-related adverse reactions reported during clinical trials with PegIntron in combination with ribavirin in adults, seen in more than half of the study subjects, were fatigue, headache, and injection site reaction. Additional adverse reactions reported in more than 25 % of subjects included nausea, chills, insomnia, anaemia, pyrexia, myalgia, asthenia, pain, alopecia, anorexia, weight decreased, depression, rash and irritability. The most frequently reported adverse reactions were mostly mild to moderate in severity and were manageable without the need for modification of doses or discontinuation of therapy. Fatigue, alopecia, pruritus, nausea, anorexia, weight decreased, irritability and insomnia occur at a notably lower rate in patients treated with PegIntron monotherapy compared to those treated with combination therapy (see **Table 4**).

The following treatment-related adverse reactions were reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron/ribavirin. These reactions are listed in **table 4** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

| **Table 4** | **Adverse reactions reported in clinical trials or through post-marketing surveillance in patients treated with peginterferon alfa-2b, including PegIntron monotherapy or PegIntron + ribavirin** |
|---|---|
| **Infections and infestations** | |
| Very common: | Viral infection*, pharyngitis* |
| Common: | Bacterial infection (including sepsis), fungal infection, influenza, upper respiratory tract infection, bronchitis, herpes simplex, sinusitis, otitis media, rhinitis |
| Uncommon: | Injection site infection, lower respiratory tract infection |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, neutropenia |
| Common: | Haemolytic anaemia, leukopenia, thrombocytopenia, lymphadenopathy |
| Very rare: | Aplastic anaemia |
| Not known: | Aplasia pure red cell |
| **Immune system disorders** | |
| Uncommon: | Drug hypersensitivity |
| Rare: | Sarcoidosis |
| Not known: | Acute hypersensitivity reactions including angioedema, anaphylaxis and anaphylactic reactions including anaphylactic shock, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, systemic lupus erythematosus |
| **Endocrine disorders** | |
| Common: | Hypothyroidism, hyperthyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia |
| Common: | Hypocalcemia, hyperuricemia, dehydration, increased appetite |
| Uncommon: | Diabetes mellitus, hypertriglyceridaemia |
| Rare: | Diabetic ketoacidosis |
| **Psychiatric disorders** | |
| Very common: | Depression, anxiety*, emotional lability*, concentration impaired, insomnia |
| Common: | Aggression, agitation, anger, mood altered, abnormal behaviour, nervousness, sleep disorder, libido decreased, apathy, abnormal dreams, crying |
| Uncommon: | Suicide, suicide attempt, suicidal ideation, psychosis, hallucination, panic attack |
| Rare: | Bipolar disorders |
| Not known: | Homicidal ideation, mania |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Amnesia, memory impairment, syncope, migraine, ataxia, confusion, neuralgia, paraesthesia, hypoaesthesia, hyperaesthesia, hypertonia, somnolence, disturbance in attention, tremor, dysgeusia |
| Uncommon: | Neuropathy, neuropathy peripheral |
| Rare: | Convulsion |
| Very rare: | Cerebrovascular haemorrhage, cerebrovascular ischaemia, encephalopathy |
| Not known: | Facial palsy, mononeuropathies |
| **Eye disorders** | |

| | |
|---|---|
| Common: | Visual disturbance, vision blurred, photophobia, conjunctivitis, eye irritation, lacrimal disorder, eye pain, dry eye |
| Uncommon: | Retinal exudates |
| Rare: | Loss of visual acuity or visual fields, retinal haemorrhage, retinopathy, retinal artery occlusion, retinal vein occlusion, optic neuritis, papilloedema, macular oedema |
| **Ear and labyrinth disorders** | |
| Common: | Hearing impaired/loss, tinnitus, vertigo |
| Uncommon | Ear pain |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| Uncommon: | Myocardial infarction |
| Rare: | Congestive heart failure, cardiomyopathy, arrhythmia, pericarditis |
| Very rare: | Cardiac ischaemia |
| Not known: | Pericardial effusion |
| **Vascular disorders** | |
| Common: | Hypotension, hypertension, flushing |
| Rare: | Vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | |
| Very common: | Dyspnoea*, cough* |
| Common: | Dysphonia, epistaxis, respiratory disorder, respiratory tract congestion, sinus congestion, nasal congestion, rhinorrhea, increased upper airway secretion, pharyngolaryngeal pain |
| Very rare: | Interstitial lung disease |
| **Gastrointestinal disorders** | |
| Very common: | Vomiting*, nausea, abdominal pain, diarrhoea, dry mouth* |
| Common: | Dyspepsia, gastroesophageal reflux disease, stomatitis, mouth ulceration, glossodynia, gingival bleeding, constipation, flatulence, haemorrhoids, cheilitis, abdominal distension, gingivitis, glossitis, tooth disorder |
| Uncommon: | Pancreatitis, oral pain |
| Rare: | Colitis ischaemic |
| Very rare: | Colitis ulcerative |
| **Hepatobiliary disorders** | |
| Common: | Hyperbilirubinemia, hepatomegaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, pruritus*, dry skin*, rash* |
| Common: | Psoriasis, photosensitivity reaction, rash maculo-papular, dermatitis, erythematous rash, eczema, night sweats, hyperhidrosis, acne, furuncle, erythema, urticaria, abnormal hair texture, nail disorder |
| Rare: | Cutaneous sarcoidosis |
| Very rare: | Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia, musculoskeletal pain |
| Common: | Arthritis, back pain, muscle spasms, pain in extremity |
| Uncommon: | Bone pain, muscle weakness |
| Rare: | Rhabdomyolysis, myositis, rheumatoid arthritis |
| **Renal and urinary disorders** | |
| Common: | Micturition frequency, polyuria, urine abnormality |
| Rare: | Renal failure, renal insufficiency |

| | |
|---|---|
| **Reproductive system and breast disorders** | |
| Common: | Amenorrhoea, breast pain, menorrhagia, menstrual disorder, ovarian disorder, vaginal disorder, sexual dysfunction, prostatitis, erectile dysfunction |
| **General disorders and administration site conditions** | |
| Very common: | Injection site reaction*, injection site inflammation, fatigue, asthenia, irritability, chills, pyrexia, influenza like illness, pain |
| Common: | Chest pain, chest discomfort, injection site pain, malaise, face oedema, oedema peripheral, feeling abnormal, thirst |
| Rare: | Injection site necrosis |
| **Investigations** | |
| Very common: | Weight decreased |

*These adverse reactions were common (≥1/100 to < 1/10) in clinical trials in patients treated with PegIntron monotherapy.

Most cases of neutropenia and thrombocytopenia were mild (WHO grades 1 or 2). There were some cases of more severe neutropenia in patients treated with the recommended doses of PegIntron in combination with ribavirin (WHO grade 3: 39 of 186 [21 %]; and WHO grade 4: 13 of 186 [7 %]).

In a clinical trial, approximately 1.2 % of patients treated with PegIntron or interferon alfa-2b in combination with ribavirin reported life-threatening psychiatric events during treatment. These events included suicidal ideation and attempted suicide (see section 4.4).

Cardiovascular (CVS) adverse events, particularly arrhythmia, appeared to be correlated mostly with pre-existing CVS disease and prior therapy with cardiotoxic agents (see section 4.4). Cardiomyopathy, that may be reversible upon discontinuation of interferon alpha, has been reported rarely in patients without prior evidence of cardiac disease.

Ophthalmological disorders that have been reported rarely with alpha interferons include retinopathies (including macular oedema), retinal haemorrhages, retinal artery or vein occlusion, retinal exudates, loss of visual acuity or visual field, optic neuritis, and papilloedema (see section 4.4).

A wide variety of autoimmune and immune-mediated disorders have been reported with alpha interferons including thyroid disorders, systemic lupus erythematosus, rheumatoid arthritis (new or aggravated), idiopathic and thrombotic thrombocytopenic purpura, vasculitis, neuropathies including mononeuropathies and Vogt-Koyanagi-Harada syndrome (see also section 4.4, Autoimmune disorders).

HCV/HIV co-infected patients

For HCV/HIV co-infected patients receiving PegIntron in combination with ribavirin, other undesirable effects (that were not reported in mono-infected patients) which have been reported in the larger studies with a frequency > 5 % were: oral candidiasis (14 %), lipodystrophy acquired (13 %), CD4 lymphocytes decreased (8 %), appetite decreased (8 %), gamma-glutamyltransferase increased (9 %), back pain (5 %), blood amylase increased (6 %), blood lactic acid increased (5 %), cytolytic hepatitis (6 %), lipase increased (6 %) and pain in limb (6 %).

*Mitochondrial toxicity:*

Mitochondrial toxicity and lactic acidosis have been reported in HIV-positive patients receiving NRTI regimen and associated ribavirin for co-HCV infection (see section 4.4).

*Laboratory values for HCV/HIV co-infected patients:*

Although haematological toxicities of neutropenia, thrombocytopenia and anaemia occurred more frequently in HCV/HIV co-infected patients, the majority could be managed by dose modification and rarely required premature discontinuation of treatment (see section 4.4). Haematological abnormalities were more frequently reported in patients receiving PegIntron in combination with ribavirin when compared to patients receiving interferon alfa-2b in combination with ribavirin. In Study 1 (see section 5.1), decrease in absolute neutrophil count levels below 500 cells/$mm^3$ was observed in 4 % (8/194) of

patients and decrease in platelets below 50,000/mm$^3$ was observed in 4 % (8/194) of patients receiving PegIntron in combination with ribavirin. Anaemia (hemoglobin < 9.4g/dl) was reported in 12% (23/194) of patients treated with PegIntron in combination with ribavirin.

*CD4 lymphocytes decrease:*
Treatment with PegIntron in combination with ribavirin was associated with decreases in absolute CD4+ cell counts within the first 4 weeks without a reduction in CD4+ cell percentage. The decrease in CD4+ cell counts was reversible upon dose reduction or cessation of therapy. The use of PegIntron in combination with ribavirin had no observable negative impact on the control of HIV viraemia during therapy or follow-up. Limited safety data (N= 25) are available in co-infected patients with CD4+ cell counts < 200/µl (see section 4.4).

Please refer to the respective Summary of Product Characteristics of the antiretroviral medicinal products that are to be taken concurrently with HCV therapy for awareness and management of toxicities specific for each product and the potential for overlapping toxicities with PegIntron in combination with ribavirin.

*Paediatric patients*
In a clinical trial with 107 children and adolescent patients (3 to 17 years of age) treated with combination therapy of PegIntron and ribavirin, dose modifications were required in 25 % of patients, most commonly for anaemia, neutropenia and weight loss. In general, the adverse reactions profile in children and adolescents was similar to that observed in adults, although there is a paediatric-specific concern regarding growth inhibition. During combination therapy for up to 48 weeks with PegIntron and ribavirin, growth inhibition is observed, the reversibility of which is uncertain (see section 4.4). Weight loss and growth inhibition were very common during the treatment (at the end of treatment, mean decrease from baseline in weight and height percentile were of 15 percentiles and 8 percentiles, respectively) and growth velocity was inhibited (< 3$^{rd}$ percentile in 70 % of the patients).

At the end of 24 weeks post-treatment follow-up, mean decrease from baseline in weight and height percentiles were still of 3 percentiles and 7 percentiles respectively, and 20 % of the children continued to have inhibited growth (growth velocity < 3$^{rd}$ percentile). Based on interim data from the long-term follow-up portion of this study, 22 % (16/74) of children had a >15 percentile decrease in height percentile, of whom 3 (4 %) children had a > 30 percentile decrease despite being off treatment for more than 1 year. In particular, decrease in mean height percentile at year 1 of long-term follow-up was most prominent in prepubertal age children (see section 4.4).

In this study, the most prevalent adverse reactions in all subjects were pyrexia (80 %), headache (62 %), neutropenia (33 %), fatigue (30 %), anorexia (29 %) and injection-site erythema (29 %). Only 1 subject discontinued therapy as the result of an adverse reaction (thrombocytopenia). The majority of adverse reactions reported in the study were mild or moderate in severity. Severe adverse reactions were reported in 7 % (8/107) of all subjects and included injection site pain (1 %), pain in extremity (1 %), headache (1 %), neutropenia (1 %), and pyrexia (4 %). Important treatment-emergent adverse reactions that occurred in this patient population were nervousness (8 %), aggression (3 %), anger (2 %), depression/depressed mood (4 %) and hypothyroidism (3 %) and 5 subjects received levothyroxine treatment for hypothyroidism/elevated TSH.

The following treatment-related adverse reactions were reported in the study in children and adolescent patients treated with PegIntron in combination with ribavirin. These reactions are listed in **Table 5** by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) or not known (cannot be estimated from the available data).
Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

| **Table 5 Adverse reactions very commonly, commonly and uncommonly reported in the clinical trial in children and adolescent patients treated with PegIntron in combination with ribavirin** | |
|---|---|
| **Infections and infestations** | |
| Common: | Fungal infection, influenza, oral herpes, otitis media, pharyngitis |

| | |
|---|---|
| | streptococcal, nasopharyngitis, sinusitis |
| Uncommon: | Pneumonia, ascariasis, enterobiasis, herpes zoster, cellulitis, urinary tract infection, gastroenteritis |
| **Blood and lymphatic system disorders** | |
| Very common: | Anaemia, leucopenia, neutropenia |
| Common: | Thrombocytopenia, lymphadenopathy |
| **Endocrine disorders** | |
| Common: | Hypothyroidism |
| **Metabolism and nutrition disorders** | |
| Very common: | Anorexia, decreased appetite |
| **Psychiatric disorders** | |
| Common: | Depression, aggression, affect lability, anger, agitation, anxiety, mood altered, restlessness, nervousness, insomnia |
| Uncommon: | Abnormal behaviour, depressed mood, emotional disorder, fear, nightmare |
| **Nervous system disorders** | |
| Very common: | Headache, dizziness |
| Common: | Dysgeusia, syncope, disturbance in attention, somnolence, poor quality sleep |
| Uncommon: | Neuralgia, lethargy, paraesthesia, hypoaesthesia, psychomotor hyperactivity, tremor |
| **Eye disorders** | |
| Common: | Eye pain |
| Uncommon: | Conjunctival haemorrhage, eye pruritus, keratitis, vision blurred, photophobia |
| **Ear and labyrinth disorders** | |
| Common: | Vertigo |
| **Cardiac disorders** | |
| Common: | Palpitations, tachycardia |
| **Vascular disorders** | |
| Common: | Flushing |
| Uncommon: | Hypotension, pallor |
| **Respiratory, thoracic and mediastinal disorders** | |
| Common: | Cough, epistaxis, pharyngolaryngeal pain |
| Uncommon: | Wheezing, nasal discomfort, rhinorrhoea |
| **Gastrointestinal disorders** | |
| Very common: | Abdominal pain, abdominal pain upper, vomiting, nausea |
| Common: | Diarrhoea, aphthous stomatitis, cheilosis, mouth ulceration, stomach discomfort, oral pain |
| Uncommon: | Dyspepsia, gingivitis |
| **Hepatobiliary disorders** | |
| Uncommon: | Hepatomagaly |
| **Skin and subcutaneous tissue disorders** | |
| Very common: | Alopecia, dry skin |
| Common: | Pruritus, rash, rash erythematous, eczema, acne, erythema |
| Uncommon: | Photosensitivity reaction, rash maculo-papular, skin exfoliation, pigmentation disorder, dermatitis atopic, skin discolouration |
| **Musculoskeletal and connective tissue disorders** | |
| Very common: | Myalgia, arthralgia |

| | |
|---|---|
| Common: | Musculoskeletal pain, pain in extremity, back pain |
| Uncommon: | Muscle contracture, muscle twitching |
| **Renal and urinary disorders** | |
| Uncommon: | Proteinuria |
| **Reproductive system and breast disorders** | |
| Uncommon: | Female: Dysmenorrhoea |
| **General disorders and administration site conditions** | |
| Very common: | Injection site erythema, fatigue, pyrexia, rigors, influenza-like illness, asthenia, pain, malaise, irritability |
| Common: | Injection site reaction, injection site pruritus, injection site rash injection site dryness, injection site pain, feeling cold |
| Uncommon: | Chest pain, chest discomfort, facial pain |
| **Investigations** | |
| Very common: | Weight decreased |
| Common: | Blood thyroid stimulating hormone increased, thyroglobulin increased |
| Uncommon: | Anti-thyroid antibody positive |
| **Injury and poisoning** | |
| Uncommon: | Contusion |

Most of the changes in laboratory values in the PegIntron/ribavirin clinical trial were mild or moderate. Decreases in haemoglobin, white blood cells, platelets, neutrophils and increase in bilirubin may require dose reduction or permanent discontinuation from therapy (see section 4.2). While changes in laboratory values were observed in some patients treated with PegIntron used in combination with ribavirin in the clinical trial, values returned to baseline levels within a few weeks after the end of therapy.

### 4.9 Overdose

Doses up to 10.5 times the intended dose have been reported. The maximum daily dose reported is 1,200 µg for one day. In general, the adverse events seen in overdose cases involving PegIntron are consistent with the known safety profile for PegIntron; however, the severity of the events may be increased. Standard methods to increase elimination of the medicinal product, e.g., dialysis, have not been shown to be useful. No specific antidote for PegIntron is available; therefore, symptomatic treatment and close observation of the patient are recommended in cases of overdose. If available, prescribers are advised to consult with a poison control centre (PCC).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Interferons, ATC code: L03AB10.

Recombinant interferon alfa-2b is covalently conjugated with monomethoxy polyethylene glycol at an average degree of substitution of 1 mole of polymer/mole of protein. The average molecular mass is approximately 31,300 daltons of which the protein moiety constitutes approximately 19,300.

- *Interferon alfa-2b*

*In vitro* and *in vivo* studies suggest that the biological activity of PegIntron is derived from its interferon alfa-2b moiety.

Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Studies with other interferons have demonstrated species specificity. However, certain monkey

species, e.g., Rhesus monkeys are susceptible to pharmacodynamic stimulation upon exposure to human type 1 interferons.

Once bound to the cell membrane, interferon initiates a complex sequence of intracellular events that include the induction of certain enzymes. It is thought that this process, at least in part, is responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells. Any or all of these activities may contribute to interferon's therapeutic effects.

Recombinant interferon alfa-2b also inhibits viral replication *in vitro* and *in vivo*. Although the exact antiviral mode of action of recombinant interferon alfa-2b is unknown, it appears to alter the host cell metabolism. This action inhibits viral replication or if replication occurs, the progeny virions are unable to leave the cell.

- *PegIntron*

PegIntron pharmacodynamics were assessed in a rising single-dose trial in healthy subjects by examining changes in oral temperature, concentrations of effector proteins such as serum neopterin and 2'5'-oligoadenylate synthetase (2'5'-OAS), as well as white cell and neutrophil counts. Subjects treated with PegIntron showed mild dose-related elevations in body temperature. Following single doses of PegIntron between 0.25 and 2.0 micrograms/kg/week, serum neopterin concentration was increased in a dose-related manner. Neutrophil and white cell count reductions at the end of week 4 correlated with the dose of PegIntron.

*PegIntron clinical trials – adults*

- Naïve patients

Two pivotal trials have been conducted, one (C/I97-010) with PegIntron monotherapy; the other (C/I98-580) with PegIntron in combination with ribavirin. Eligible patients for these trials had chronic hepatitis C confirmed by a positive HCV-RNA polymerase chain reaction (PCR) assay (> 30 IU/ml), a liver biopsy consistent with a histological diagnosis of chronic hepatitis with no other cause for the chronic hepatitis, and abnormal serum ALT.

In the PegIntron monotherapy trial, a total of 916 naïve chronic hepatitis C patients were treated with PegIntron (0.5, 1.0 or 1.5 micrograms/kg/week) for one year with a follow-up period of six months. In addition, 303 patients received interferon alfa-2b (3 million International Units [MIU] three times a week) as a comparator. This study showed that PegIntron was superior to interferon alfa-2b (**Table 6**).

In the PegIntron combination trial, 1,530 naïve patients were treated for one year with one of the following combination regimens:

- PegIntron (1.5 micrograms/kg/week) + ribavirin (800 mg/day), (n = 511).
- PegIntron (1.5 micrograms/kg/week for one month followed by 0.5 microgram/kg/week for 11 months) + ribavirin (1,000/1,200 mg/day), (n = 514).
- Interferon alfa-2b (3 MIU three times a week) + ribavirin (1,000/1,200 mg/day) (n = 505).

In this trial, the combination of PegIntron (1.5 micrograms/kg/week) and ribavirin was significantly more effective than the combination of interferon alfa-2b and ribavirin (**Table 6**), particularly in patients infected with Genotype 1 (**Table 7**). Sustained response was assessed by the response rate six months after the cessation of treatment.

HCV genotype and baseline virus load are prognostic factors which are known to affect response rates. However, response rates in this trial were shown to be dependent also on the dose of ribavirin administered in combination with PegIntron or interferon alfa-2b. In those patients that received > 10.6 mg/kg ribavirin (800 mg dose in typical 75 kg patient), regardless of genotype or viral load, response rates were significantly higher than in those patients that received ≤ 10.6 mg/kg ribavirin (**Table 7**), while response rates in patients that received > 13.2 mg/kg ribavirin were even higher.

| Table 6 Sustained virological response (% patients HCV negative) | | | | | | | |
|---|---|---|---|---|---|---|---|
| | PegIntron monotherapy | | | | PegIntron + ribavirin | | |
| **Treatment regimen** | **P 1.5** | **P 1.0** | **P 0.5** | **I** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **Number of patients** | 304 | 297 | 315 | 303 | 511 | 514 | 505 |
| **Response at end of treatment** | 49 % | 41 % | 33 % | 24 % | 65 % | 56 % | 54 % |
| **Sustained response** | **23 %*** | **25 %** | **18 %** | **12 %** | **54 %**** | **47 %** | **47 %** |

P 1.5 PegIntron 1.5 micrograms/kg
P 1.0 PegIntron 1.0 microgram/kg
P 0.5 PegIntron 0.5 microgram/kg
I Interferon alfa-2b 3 MIU
P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)
* $p < 0.001$ P 1.5 vs. I
** $p = 0.0143$ P 1.5/R vs. I/R

| Table 7 Sustained response rates with PegIntron + ribavirin (by ribavirin dose, genotype and viral load) | | | | |
|---|---|---|---|---|
| **HCV Genotype** | **Ribavirin dose (mg/kg)** | **P 1.5/R** | **P 0.5/R** | **I/R** |
| **All Genotypes** | **All** | **54 %** | **47 %** | **47 %** |
| | ≤ 10.6 | 50 % | 41 % | 27 % |
| | > 10.6 | 61 % | 48 % | 47 % |
| **Genotype 1** | **All** | **42 %** | **34 %** | **33 %** |
| | ≤ 10.6 | 38 % | 25 % | 20 % |
| | > 10.6 | 48 % | 34 % | 34 % |
| Genotype 1 ≤ 600,000 IU/ml | All | 73 % | 51 % | 45 % |
| | ≤ 10.6 | 74 % | 25 % | 33 % |
| | > 10.6 | 71 % | 52 % | 45 % |
| Genotype 1 > 600,000 IU/ml | All | 30 % | 27 % | 29 % |
| | ≤ 10.6 | 27 % | 25 % | 17 % |
| | > 10.6 | 37 % | 27 % | 29 % |
| **Genotype 2/3** | **All** | **82 %** | **80 %** | **79 %** |
| | ≤ 10.6 | 79 % | 73 % | 50 % |
| | > 10.6 | 88 % | 80 % | 80 % |

P 1.5/R PegIntron (1.5 micrograms/kg) + ribavirin (800 mg)
P 0.5/R PegIntron (1.5 to 0.5 microgram/kg) + ribavirin (1,000/1,200 mg)
I/R Interferon alfa-2b (3 MIU) + ribavirin (1,000/1,200 mg)

In the PegIntron monotherapy study, the Quality of Life was generally less affected by 0.5 microgram/kg of PegIntron than by either 1.0 microgram/kg of PegIntron once weekly or 3 MIU of interferon alfa-2b three times a week.

In a separate trial, 224 patients with genotype 2 or 3 received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with ribavirin 800 mg –1,400 mg p.o. for 6 months (based on body weight, only three patients weighing > 105 kg, received the 1,400 mg dose) (**Table 8**). Twenty-four % had bridging fibrosis or cirrhosis (Knodell 3/4).

| Table 8 Virologic response at end of treatment, Sustained Virologic Response and relapse by HCV Genotype and viral load* | | | |
|---|---|---|---|
| | PegIntron 1.5 µg/kg once weekly plus Ribavirin 800-1,400 mg/day | | |
| | End of treatment response | Sustained Virologic Response | Relapse |

| | | | |
|---|---|---|---|
| All subjects | 94 % (211/224) | 81 % (182/224) | 12 % (27/224) |
| HCV 2 | 100 % (42/42) | 93 % (39/42) | 7 % (3/42) |
| ≤ 600,000 IU/ml | 100 % (20/20) | 95 % (19/20) | 5 % (1/20) |
| > 600,000 IU/ml | 100 % (22/22) | 91 % (20/22) | 9 % (2/22) |
| HCV 3 | 93 % (169/182) | 79 % (143/182) | 14 % (24/166) |
| ≤ 600,000 IU/ml | 93 % (92/99) | 86 % (85/99) | 8 % (7/91) |
| > 600,000 IU/ml | 93 % (77/83) | 70 % (58/83) | 23 % (17/75) |

* Any subject with an undetectable HCV-RNA level at the follow-up week 12 visit and missing data at the follow-up week 24 visit was considered a sustained responder. Any subject with missing data in and after the follow-up week 12 window was considered to be a non-responder at week 24 of follow-up.

The 6 month treatment duration in this trial was better tolerated than one year of treatment in the pivotal combination trial; for discontinuation 5 % vs. 14 %, for dose modification 18 % vs. 49 %.

In a non-comparative trial, 235 patients with genotype 1 and low viral load (< 600,000 IU/ml) received PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. The overall sustained response rate after a 24-week treatment duration was 50 %. Forty-one percent of subjects (97/235) had nondetectable plasma HCV-RNA levels at week 4 and week 24 of therapy. In this subgroup, there was a 92 % (89/97) sustained virological response rate. The high sustained response rate in this subgroup of patients was identified in an interim analysis (n=49) and prospectively confirmed (n=48).
Limited historical data indicate that treatment for 48 weeks might be associated with a higher sustained response rate (11/11) and with a lower risk of relapse (0/11 as compared to 7/96 following 24 weeks of treatment).

A large randomized trial compared the safety and efficacy of treatment for 48 weeks with two PegIntron/ribavirin regimens [PegIntron 1.5 µg/kg and 1 µg/kg subcutaneously once weekly both in combination with ribavirin 800 to 1,400 mg p.o. daily (in two divided doses)] and peginterferon alfa-2a 180 µg subcutaneously once weekly with ribavirin 1,000 to 1,200 mg p.o. daily (in two divided doses) in 3,070 treatment-naïve adults with chronic hepatitis C genotype 1. Response to the treatment was measured by Sustained Virologic Response (SVR) which is defined as undetectable HCV-RNA at 24 weeks post-treatment (see **Table 9**).

| Table 9 Virologic response at treatment week 12, end of treatment response, relapse rate *and Sustained Virologic Response (SVR) | | | |
|---|---|---|---|
| Treatment group | % (number) of patients | | |
| | PegIntron 1.5 µg/kg + ribavirin | PegIntron 1 µg/kg + ribavirin | peginterferon alfa-2a 180 µg + ribavirin |
| Undetectable HCV-RNA at treatment week 12 | 40 (407/1,019) | 36 (366/1,016) | 45 (466/1,035) |
| End of treatment response | 53 (542/1,019) | 49 (500/1,016) | 64 (667/1,035) |
| Relapse | 24 (123/523) | 20 (95/475) | 32 (193/612) |
| SVR | 40 (406/1,019) | 38 (386/1,016) | 41 (423/1,035) |
| SVR in patients with undetectable HCV-RNA at treatment week 12 | 81 (328/407) | 83 (303/366) | 74 (344/466) |

* (HCV-RNA PCR assay, with a lower limit of quantitation of 27 IU/ml)
Lack of early virologic response by Treatment week 12 (detectable HCV-RNA with a < 2 $\log_{10}$ reduction from baseline) was a criterion for discontinuation of treatment.

In all three treatment groups, sustained virologic response rates were similar. In patients of African American origin (which is known to be a poor prognostic factor for HCV eradication), treatment with PegIntron (1.5 µg/kg)/ribavirin combination therapy resulted in a higher sustained virologic response rate compared to PegIntron 1 µg/kg dose. At the PegIntron 1.5 µg/kg plus ribavirin dose, sustained virologic response rates were lower in patients with cirrhosis, in patients with normal ALT levels, in patients with a baseline viral load > 600,000 IU/ml, and in patients > 40 years old. Caucasian patients had a higher sustained virologic response rate compared to the African Americans. Among patients with undetectable HCV-RNA at the end of treatment, the relapse rate was 24 %.

*Predictability of sustained virological response – Naïve patients*
Virological response by week 12 is defined as at least 2-log viral load decrease or undetectable levels of HCV-RNA.Virological response by week 4 is defined as at least 1-log viral load decrease or undetectable levels of HCV-RNA. These time points (treatment week 4 and treatment week 12) have been shown to be predictive for sustained response (**Table 10**).

| **Table 10 Predictive value of in-treatment Virologic Response while on PegIntron 1.5 µg/kg/ribavirin 800-1,400 mg combination therapy** | | | | | | |
|---|---|---|---|---|---|---|
| | **Negative** | | | **Positive** | | |
| | No response at treatment week | No sustained response | Negative predictive value | Response at treatment week | Sustained response | Positive predictive value |
| **Genotype 1*** | | | | | | |
| ***By week 4****** **(n=950)** | | | | | | |
| HCV-RNA negative | 834 | 539 | **65 %** (539/834) | 116 | 107 | **92 %** (107/116) |
| HCV-RNA negative or ≥ 1 log decrease in viral load | 220 | 210 | **95 %** (210/220) | 730 | 392 | **54 %** (392/730) |
| ***By week 12****** **(n=915*)*** | | | | | | |
| HCV-RNA negative | 508 | 433 | **85 %** (433/508) | 407 | 328 | **81 %** (328/407) |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 206 | 205 | **N/A**[†] | 709 | 402 | **57 %** (402/709) |
| **Genotype 2, 3**** | | | | | | |
| ***By week 12*** **(n= 215)** | | | | | | |
| HCV-RNA negative or ≥ 2 log decrease in viral load | 2 | 1 | **50 %** (1/2) | 213 | 177 | **83 %** (177/213) |

*Genotype 1 receive 48 weeks treatment

**Genotype 2, 3 receive 24 weeks treatment

***The presented results are from a single point of time. A patient may be missing or have had a different result for week 4 or week 12.

[†] These criteria were used in the protocol: If week 12 HCV-RNA is positive and < $2\log_{10}$ decrease from baseline, patients to stop therapy. If week 12 HCV-RNA is positive and decreased ≥ $2\log_{10}$ from baseline, then retest HCV-RNA at week 24 and if positive, patients to stop therapy.

The negative predictive value for sustained response in patients treated with PegIntron in monotherapy was 98 %.

HCV/HIV Co-infected patients

Two trials have been conducted in patients co-infected with HIV and HCV. The response to treatment in both of these trials is presented in **Table11.** Study 1 (RIBAVIC; P01017) was a randomized, multicentre study which enrolled 412 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (1.5 µg/kg/week) plus ribavirin (800 mg/day) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800 mg/day) for 48 weeks with a follow-up period of 6 months. Study 2 (P02080) was a randomized, single centre study that enrolled 95 previously untreated adult patients with chronic hepatitis C who were co-infected with HIV. Patients were randomized to receive either PegIntron (100 or 150 µg /week based on weight) plus ribavirin (800-1,200 mg/day based on weight) or interferon alfa-2b (3 MIU TIW) plus ribavirin (800-1,200 mg/day based on weight). The duration of therapy was 48 weeks with a follow-up

period of 6 months except for patients infected with genotypes 2 or 3 and viral load < 800,000 IU/ml (Amplicor) who were treated for 24 weeks with a 6-month follow-up period.

| **Table11** | **Sustained virological response based on genotype after PegIntron in combination with Ribavirin in HCV/HIV Co-infected patients** | | | | | |
|---|---|---|---|---|---|---|
| | **Study 1**[1] | | | **Study 2**[2] | | |
| | PegIntron (1.5 µg/kg/ week) + ribavirin (800 mg) | Interferon alfa-2b (3 MIU TIW) + ribavirin (800 mg) | p value[a] | PegIntron (100 or 150[c] µg/week) + ribavirin (800-1,200 mg)[d] | Interferon alfa-2b (3 MIU TIW) + ribavirin (800-1,200 mg)[d] | p value[b] |
| All | 27 % (56/205) | 20 % (41/205) | 0.047 | 44 % (23/52) | 21 % (9/43) | 0.017 |
| Genotype 1, 4 | 17 % (21/125) | 6 % (8/129) | 0.006 | 38 % (12/32) | 7 % (2/27) | 0.007 |
| Genotype 2, 3 | 44 % (35/80) | 43 % (33/76) | 0.88 | 53 % (10/19) | 47 % (7/15) | 0.730 |

MIU = million international units; TIW = three times a week.
a: p value based on Cochran-Mantel Haenszel Chi square test.
b: p value based on chi-square test.
c: subjects < 75 kg received 100 µg/week PegIntron and subjects ≥ 75 kg received 150 µg/week PegIntron.
d: ribavirin dosing was 800 mg for patients < 60 kg, 1,000 mg for patients 60-75 kg, and 1,200 mg for patients > 75 kg.

[1]Carrat F, Bani-Sadr F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
[2] Laguno M, Murillas J, Blanco J.L et al. AIDS 2004; 18(13): F27-F36.

*Histological response*
Liver biopsies were obtained before and after treatment in Study 1 and were available for 210 of the 412 subjects (51 %). Both the Metavir score and Ishak grade decreased among subjects treated with PegIntron in combination with ribavirin. This decline was significant among responders (-0.3 for Metavir and -1.2 for Ishak) and stable (-0.1 for Metavir and -0.2 for Ishak) among non-responders. In terms of activity, about one-third of sustained responders showed improvement and none showed worsening. There was no improvement in terms of fibrosis observed in this study. Steatosis was significantly improved in patients infected with HCV Genotype 3.

- PegIntron/ribavirin retreatment of prior treatment failures

In a non-comparative trial, 2,293 patients with moderate to severe fibrosis who failed previous treatment with combination alpha interferon/ribavirin were retreated with PegIntron, 1.5 micrograms/kg subcutaneously, once weekly, in combination with weight adjusted ribavirin. Failure to prior therapy was defined as relapse or non-response (HCV-RNA positive at the end of a minimum of 12 weeks of treatment).

Patients who were HCV-RNA negative at treatment week 12 continued treatment for 48 weeks and were followed for 24 weeks post-treatment. Response week 12 was defined as undetectable HCV-RNA after 12 weeks of treatment. Sustained Virologic Response (SVR) is defined as undetectable HCV-RNA at 24 weeks post-treatment (**Table12***)*.

**Table 12 Rates of response to retreatment in prior treatment failures**

| | Patients with undetectable HCV–RNA at treatment week 12 and SVR upon retreatement | | | | |
|---|---|---|---|---|---|
| | interferon alpha/ribavirin | | peginterferon alpha/ribavirin | | Overall population* |
| | Response week 12 % (n/N) | SVR % (n/N) 99% CI | Response week 12 % (n/N) | SVR % (n/N) 99% CI | SVR % (n/N) 99 % CI |
| Overall | 38.6 (549/1,423) | 59.4 (326/549) 54.0,64.8 | 31.5 (272/863) | 50.4 (137/272) 42.6, 58.2 | 21.7 (497/2,293) 19.5, 23.9 |
| Prior response | | | | | |
| Relapse | 67.7 (203/300) | 59.6 (121/203) 50.7, 68.5 | 58.1 (200/344) | 52.5 (105/200) 43.4, 61.6 | 37.7 (243/645) 32.8, 42.6 |
| Genotype 1/4 | 59.7 (129/216) | 51.2 (66/129) 39.8, 62.5 | 48.6 (122/251) | 44.3 (54/122) 32.7, 55.8 | 28.6 (134/468) 23.3, 34.0 |
| Genotype 2/3 | 88.9 (72/81) | 73.6 (53/72) (60.2, 87.0) | 83.7 (77/92) | 64.9 (50/77) 50.9, 78.9 | 61.3 (106/173) 51.7, 70.8 |
| NR | 28.6 (258/903) | 57.0 (147/258) 49.0, 64.9 | 12.4 (59/476) | 44.1 (26/59) 27.4, 60.7 | 13.6 (188/1,385) 11.2, 15.9 |
| Genotype 1/4 | 23.0 (182/790) | 51.6 (94/182) 42.1, 61.2 | 9.9 (44/446) | 38.6 (17/44) 19.7, 57.5 | 9.9 (123/1,242) 7.7, 12.1 |
| Genotype 2/3 | 67.9 (74/109) | 70.3 (52/74) 56.6, 84.0 | 53.6 (15/28) | 60.0 (9/15) 27.4, 92.6 | 46.0 (63/137) 35.0, 57.0 |
| Genotype | | | | | |
| 1 | 30.2 (343/1,135) | 51.3 (176/343) 44.4, 58.3 | 23.0 (162/704) | 42.6 (69/162) 32.6, 52.6 | 14.6 (270/1,846) 12.5, 16.7 |
| 2/3 | 77.1 (185/240) | 73.0 (135/185) 64.6, 81.4 | 75.6 (96/127) | 63.5 (61/96) 50.9, 76.2 | 55.3 (203/367) 48.6, 62.0 |
| 4 | 42.5 (17/40) | 70.6 (12/17) 42.1, 99.1 | 44.4 (12/27) | 50.0 (6/12) 12.8, 87.2 | 28.4 (19/67) 14.2, 42.5 |
| METAVIR Fibrosis score | | | | | |
| F2 | 46.0 (193/420) | 66.8 (129/193) 58.1, 75.6 | 33.6 (78/232) | 57.7 (45/78) 43.3, 72.1 | 29.2 (191/653) 24.7, 33.8 |
| F3 | 38.0 (163/429) | 62.6 (102/163) 52.8, 72.3 | 32.4 (78/241) | 51.3 (40/78) 36.7, 65.9 | 21.9 (147/672) 17.8, 26.0 |
| F4 | 33.6 (192/572) | 49.5 (95/192) 40.2, 58.8 | 29.7 (116/390) | 44.8 (52/116) 32.9, 56.7 | 16.5 (159/966) 13.4, 19.5 |
| Baseline Viral Load | | | | | |
| HVL (>600,000 IU/ml) | 32.4 (280/864) | 56.1 (157/280) 48.4, 63.7 | 26.5 (152/573) | 41.4 (63/152) 31.2, 51.7 | 16.6 (239/1,441) 14.1, 19.1 |
| LVL (≤600,000 IU/ml) | 48.3 (269/557) | 62.8 (169/269) 55.2, 70.4 | 41.0 (118/288) | 61.0 (72/118) 49.5, 72.6 | 30.2 (256/848) 26.1, 34.2 |

NR: Non-responder defined as serum/plasma HCV-RNA positive at the end of a minimum of 12 weeks of treatment.
Plasma HCV-RNA is measured with a research-based quantitative polymerase chain reaction assay by a central laboratory

*Intent to treat population includes 7 patients for whom at least 12 weeks of prior therapy could not be confirmed.

Overall, approximately 36 % (821/2,286) of patients had undetectable plasma HCV-RNA levels at week 12 of therapy measured using a research-based test (limit of detection 125 IU/ml). In this subgroup, there was a 56 % (463/823) sustained virological response rate. For patients with prior failure on therapy with nonpegylated interferon or pegylated interferon and negative at week 12, the sustained response rates were 59 % and 50 %, respectively. Among 480 patients with > 2 log viral reduction but detectable virus at week 12, altogether 188 patients continued therapy. In those patients the SVR was 12 %.

Non-responders to prior therapy with pegylated interferon alpha/ribavirin were less likely to achieve a week 12 response to retreatment than non-responders to nonpegylated interferon alpha/ribavirin (12.4 % vs. 28.6 %). However, if a week 12 response was achieved, there was little difference in SVR regardless of prior treatment or prior response.

- Long-term efficacy data

A large long-term follow-up study enrolled 567 patients after treatment in a prior study with PegIntron (with or without ribavirin). The purpose of the study was to evaluate the durability of sustained virologic response (SVR) and assess the impact of continued viral negativity on clinical outcomes. 327 patients completed at least 5 years of long-term follow-up and only 3 out of 366 sustained responders relapsed during the study.
The Kaplan-Meier estimate for continued sustained response over 5 years for all patients is 99 % (95 % CI: 98-100 %). SVR after treatment of chronic HCV with PegIntron (with or without ribavirin) results in long-term clearance of the virus providing resolution of the hepatic infection and clinical "cure" from chronic HCV. However, this does not preclude the occurrence of hepatic events in patients with cirrhosis (including hepatocarcinoma).

*PegIntron clinical trials – paediatric patients*

Children and adolescents 3 to 17 years of age with compensated chronic hepatitis C and detectable HCV-RNA were enrolled in a multicentre trial and treated with ribavirin 15 mg/kg per day plus PegIntron 60 μg/m$^2$ once weekly for 24 or 48 weeks, based on HCV genotype and baseline viral load. All patients were to be followed for 24 weeks post-treatment. A total of 107 patients received treatment of whom 52 % were female, 89 % Caucasian, 67 % with HCV Genotype 1 and 63 % < 12 years of age. The population enrolled mainly consisted of children with mild to moderate hepatitis C. Due to the lack of data in children with severe progression of the disease, and the potential for undesirable effects**,** the benefit/risk of the combination of PegIntron with ribavirin needs to be carefully considered in this population (see sections 4.1, 4.4 and 4.8). The study results are summarized in **Table 13**

**Table 13 Sustained virological response rates (n[a,b] (%)) in previously untreated children and adolescents by genotype and treatment duration – All subjects**

| | **n = 107** | |
|---|---|---|
| | **24 weeks** | **48 weeks** |
| All Genotypes | 26/27 (96 %) | 44/80 (55 %) |
| Genotype 1 | - | 38/72 (53 %) |
| Genotype 2 | 14/15 (93 %) | - |
| Genotype 3[c] | 12/12 (100 %) | 2/3 (67 %) |
| Genotype 4 | - | 4/5 (80 %) |

a: Response to treatment was defined as undetectable HCV-RNA at 24 weeks post-treatment lower limit of detection=125IU/ml

b: n = number of responders/number of subjects with given genotype, and assigned treatment duration.

c: Patients with genotype 3 low viral load (< 600,000 IU/ml) were to receive 24 weeks of treatment while those with genotype 3 and high viral load (≥ 600,000 IU/ml) were to receive 48 weeks of treatment.

## 5.2 Pharmacokinetic properties

PegIntron is a well characterized polyethylene glycol-modified ("pegylated") derivative of interferon alfa-2b and is predominantly composed of monopegylated species. The plasma half-life of PegIntron is prolonged compared with nonpegylated interferon alfa-2b. PegIntron has a potential to depegylate to free interferon alfa-2b. The biologic activity of the pegylated isomers is qualitatively similar, but weaker than free interferon alfa-2b.

Following subcutaneous administration, maximal serum concentrations occur between 15-44 hours post-dose, and are sustained for up to 48-72 hours post-dose.

PegIntron $C_{max}$ and AUC measurements increase in a dose-related manner. Mean apparent volume of distribution is 0.99 l/kg.

Upon multiple dosing, there is an accumulation of immunoreactive interferons. There is, however, only a modest increase in biologic activity as measured by a bioassay.

Mean (SD) PegIntron elimination half-life is approximately 40 hours (13.3 hours), with apparent clearance of 22.0 ml/hr/kg. The mechanisms involved in clearance of interferons in man have not yet been fully elucidated. However, renal elimination may account for a minority (approximately 30 %) of PegIntron apparent clearance.

Renal function: Renal clearance appears to account for 30 % of total clearance of PegIntron. In a single dose study (1.0 microgram/kg) in patients with impaired renal function, $C_{max}$, AUC, and half-life increased in relation to the degree of renal impairment.

Following multiple dosing of PegIntron (1.0 microgram/kg subcutaneously administered every week for four weeks) the clearance of PegIntron is reduced by a mean of 17 % in patients with moderate renal impairment (creatinine clearance 30-49 ml/minute) and by a mean of 44 % in patients with severe renal impairment (creatinine clearance 15-29 ml/minute) compared to subjects with normal renal function. Based on single dose data, clearance was similar in patients with severe renal impairment not on dialysis and in patients who were receiving hemodialysis. The dose of PegIntron for monotherapy should be reduced in patients with moderate or severe renal impairment (see sections 4.2 and 4.4). Patients with creatinine clearance < 50 ml/minute must not be treated with PegIntron in combination with ribavirin (see section 4.3).

Because of marked inter-subject variability in interferon pharmacokinetics, it is recommended that patients with severe renal impairment be closely monitored during treatment with PegIntron (see section 4.2)

Hepatic function: The pharmacokinetics of PegIntron have not been evaluated in patients with severe hepatic dysfunction.

Elderly patients ≥ 65 years of age: The pharmacokinetics of PegIntron following a single subcutaneous dose of 1.0 microgram/kg were not affected by age. The data suggest that no alteration in PegIntron dosage is necessary based on advancing age.

Paediatric patients: Multiple-dose pharmacokinetic properties for PegIntron and ribavirin (capsules and oral solution) in children and adolescent patients with chronic hepatitis C have been evaluated during a clinical study. In children and adolescent patients receiving body surface area-adjusted dosing of PegIntron at 60 μg/$m^2$/week, the log transformed ratio estimate of exposure during the dosing interval is predicted to be 58 % (90 % CI: 141-177 %) higher than observed in adults receiving 1.5 μg/kg/week.

Interferon neutralising factors: Interferon neutralising factor assays were performed on serum samples of patients who received PegIntron in the clinical trial. Interferon neutralising factors are antibodies which neutralise the antiviral activity of interferon. The clinical incidence of neutralising factors in patients who

received PegIntron 0.5 micrograms/kg is 1.1 %.

### 5.3 Preclinical safety data

PegIntron: Adverse events not observed in clinical trials were not seen in toxicity studies in monkeys. These studies were limited to four weeks due to the appearance of anti-interferon antibodies in most monkeys.

Reproduction studies of PegIntron have not been performed. Interferon alfa-2b has been shown to be an abortifacient in primates. PegIntron is likely to also cause this effect. Effects on fertility have not been determined. It is not known whether the components of this medicinal product are excreted into experimental animal or human milk (see section 4.6 for relevant human data on pregnancy and lactation). PegIntron showed no genotoxic potential.

The relative non-toxicity of monomethoxy-polyethylene glycol (mPEG), which is liberated from PegIntron by metabolism *in vivo* has been demonstrated in preclinical acute and subchronic toxicity studies in rodents and monkeys, standard embryo-foetal development studies and in *in vitro* mutagenicity assays.

PegIntron plus ribavirin: When used in combination with ribavirin, PegIntron did not cause any effects not previously seen with either active substance alone. The major treatment-related change was a reversible, mild to moderate anaemia, the severity of which was greater than that produced by either active substance alone.

No studies have been conducted in juvenile animals to examine the effects of treatment with PegIntron on growth, development, sexual maturation, and behaviour. Preclinical juvenile toxicity results have demonstrated a minor, dose-related decrease in overall growth in neonatal rats dosed with ribavirin (see section 5.3 of Rebetol SPC if PegIntron is to be administered in combination with ribavirin).

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Powder for solution for injection:*
- Disodium phosphate, anhydrous
- Sodium dihydrogen phosphate dihydrate
- Sucrose
- Polysorbate 80

*Solvent:*
- Water for injections

Deliverable volume from pen = 0.5 ml.

### 6.2 Incompatibilities

This medicinal product should only be reconstituted with the solvent provided (see section 6.6). In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

*Before reconstitution:*
3 years.

*After reconstitution:*

- Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8ºC.
- From a microbiological point of view, the product is to be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C). Do not freeze.

For storage conditions of the reconstituted medicinal product, see section 6.3.

**6.5 Nature and contents of container**

The powder and solvent are both contained in a two-chamber cartridge (Type I flint glass) separated by a bromobutyl rubber plunger. The cartridge is sealed at one end with a polypropylene cap containing a bromobutyl rubber liner and at the other end by a bromobutyl rubber plunger.

PegIntron 150 micrograms is supplied as:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

Each pen is reconstituted with the solvent provided in the two-chamber cartridge (water for injections) for administration of up to 0.5 ml of solution. A small volume is lost during preparation of PegIntron for injection when the dose is measured and injected. Therefore, each pen contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection. The reconstituted solution has a concentration of 150 micrograms in 0.5 ml.

PegIntron is injected subcutaneously after reconstituting the powder as instructed, attaching an injection needle and setting the prescribed dose. A complete and illustrated set of instructions is provided in the Annex to the Package Leaflet.

PegIntron pre-filled pen is to be removed from the refrigerator before administration to allow the solvent to reach room temperature (not more than 25°C).

As for all parenteral medicinal products, the reconstituted solution should be inspected prior to administration. The reconstituted solution should be clear and colourless. If discolouration or particulate matter is present, the reconstituted solution should not be used. After administering the dose, the PegIntron pre-filled pen and any unused solution contained in it is to be discarded.

**7. MARKETING AUTHORISATION HOLDER**

SP Europe
73, rue de Stalle
B-1180 Bruxelles
Belgium

## 8. MARKETING AUTHORISATION NUMBERS

EU/1/00/131/047
EU/1/00/131/048
EU/1/00/131/049
EU/1/00/131/050

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25 May 2000
Date of latest renewal:

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the web-site of the European Medicines Agency http://www.ema.europa.eu/

# ANNEX II

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

## B. CONDITIONS OF THE MARKETING AUTHORISATION

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

SP (Brinny) Company
Innishannon - County Cork
Ireland

Name and address of the manufacturer responsible for batch release

SP Labo N.V.
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

## B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.5 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted
* When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
* Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
* At the request of the European Medicines Agency

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 50 micrograms**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 micrograms of peginterferon alfa-2b and
provides 50 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
50 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator.**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/001 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/002 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/003 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/004 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/005 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/026 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 50 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 50 micrograms – vial of powder**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 80 micrograms**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 80 micrograms of peginterferon alfa-2b and
provides 80 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
80 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator.**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/006 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/007 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/008 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/009 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/010 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/027 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 80 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 80 micrograms - vial of powder**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 100 micrograms**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 100 micrograms of peginterferon alfa-2b and
provides 100 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
100 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP
After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator.**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/011 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/012 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/013 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/014 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/015 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/028 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 100 mg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 100 micrograms - vial of powder**

## 1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 120 micrograms**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 120 micrograms of peginterferon alfa-2b and
provides 120 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
120 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator.**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/016 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/017 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/018 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/019 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/020 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/029 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 120 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 120 micrograms - vial of powder**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 150 micrograms**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 150 micrograms of peginterferon alfa-2b and
provides 150 micrograms/0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. One ampoule of solvent contains 0.7 ml of water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 vial of powder, 1 ampoule of solvent
1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab
4 vials of powder, 4 ampoules of solvent
4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs
6 vials of powder, 6 ampoules of solvent
12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs
150 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator.**

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After withdrawal of the dose, any remaining solution must be discarded.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/021 (1 vial of powder, 1 ampoule of solvent)
EU/1/00/131/022 (1 vial of powder, 1 ampoule of solvent, 1 injection syringe, 2 injection needles and 1 cleansing swab)
EU/1/00/131/023 (4 vials of powder, 4 ampoules of solvent)
EU/1/00/131/024 (4 vials of powder, 4 ampoules of solvent, 4 injection syringes, 8 injection needles and 4 cleansing swabs)
EU/1/00/131/025 (6 vials of powder, 6 ampoules of solvent)
EU/1/00/131/030 (12 vials of powder, 12 ampoules of solvent, 12 injection syringes, 24 injection needles and 12 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 150 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 150 micrograms - vial of powder**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

## 6. OTHER

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron - ampoule of solvent**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for PegIntron
Water for injections

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.7 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 50 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 50 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 50 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
50 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator**. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/031 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/032 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/033 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/034 (12 pens, 12 injection needles and 24 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 50 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 50 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 50 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 80 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 80 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 80 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
80 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator**. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/035 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/036 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/037 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/038 (12 pens, 12 injection needles and 24 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 80 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 80 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 80 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

80 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 100 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 100 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 100 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
100 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator**. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/039 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/040 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/041 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/042 (12 pens, 12 injection needles and 24 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 100 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 100 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 100 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 120 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 120 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 120 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
120 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator**. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/043 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/044 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/045 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/046 (12 pens, 12 injection needles and 24 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 120 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 120 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 120 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

120 micrograms/0.5 ml

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**Carton 150 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT

PegIntron 150 micrograms powder and solvent for solution for injection pre-filled pen
peginterferon alfa-2b

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

One PegIntron pre-filled pen contains a sufficient amount of peginterferon alfa-2b to provide 150 micrograms in 0.5 ml of peginterferon alfa-2b when reconstituted as recommended.

## 3. LIST OF EXCIPIENTS

Excipients: disodium phosphate, anhydrous; sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80. Solvent: water for injections.

## 4. PHARMACEUTICAL FORM AND CONTENTS

1 pen, 1 injection needle and 2 cleansing swabs
4 pens, 4 injection needles and 8 cleansing swabs
6 pens, 6 injection needles and 12 cleansing swabs
12 pens, 12 injection needles and 24 cleansing swabs
150 micrograms/0.5 ml

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

## 9. SPECIAL STORAGE CONDITIONS

**Store in a refrigerator**. Do not freeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

After injection of the dose, discard the pen in an appropriate container.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Marketing authorisation holder: SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/131/047 (1 pen, 1 injection needle and 2 cleansing swabs)
EU/1/00/131/048 (4 pens, 4 injection needles and 8 cleansing swabs)
EU/1/00/131/049 (6 pens, 6 injection needles and 12 cleansing swabs)
EU/1/00/131/050 (12 pens, 12 injection needles and 24 cleansing swabs)

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

PegIntron 150 mcg

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**PegIntron 150 micrograms powder and solvent for solution for injection**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

PegIntron 150 micrograms powder and solvent for injection
peginterferon alfa-2b
SC

## 2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

150 micrograms/0.5 ml

## 6. OTHER

# B. PACKAGE LEAFLET

**PACKAGE LEAFLET : INFORMATION FOR THE USER**

**PegIntron 50 micrograms powder and solvent for solution for injection**
peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. How to store PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients:*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents:*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor has told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C).

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each vial contains 50 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 50 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

**HOW TO SELF-INJECT PEGINTRON?**

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect the necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
**Change your injection site each time.**

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 80 micrograms powder and solvent for solution for injection**
peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor has told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C).

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each vial contains 80 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 80 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

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SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency
http://www.ema.europa.eu

**HOW TO SELF-INJECT PEGINTRON?**

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect the necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
**Change your injection site each time.**

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 100 micrograms powder and solvent for solution for injection**
peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*
- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C).

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each vial contains 100 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 100 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

**HOW TO SELF-INJECT PEGINTRON?**

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect the necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
**Change your injection site each time.**

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 120 micrograms powder and solvent for solution for injection**
peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C).

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each vial contains 120 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 120 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency
http://www.ema.europa.eu

**HOW TO SELF-INJECT PEGINTRON?**

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect the necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
**Change your injection site each time.**

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 150 micrograms powder and solvent for solution for injection**
peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines:**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to self-inject PegIntron at the end of the package leaflet).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. Discard any solution that is left in the vial after you give yourself the injection.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C).

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. Discard any unused material.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each vial contains 150 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection.
The white powder is contained in a 2 ml glass vial and the clear and colourless solvent is presented in a 2 ml glass ampoule.

PegIntron 150 micrograms is available in different pack sizes:
- 1 vial of powder for solution for injection and 1 ampoule of solvent for parenteral use;
- 1 vial of powder for solution for injection, 1 ampoule of solvent for parenteral use, 1 injection syringe, 2 injection needles and 1 cleansing swab;
- 4 vials of powder for solution for injection and 4 ampoules of solvent for parenteral use;
- 4 vials of powder for solution for injection, 4 ampoules of solvent for parenteral use, 4 injection syringes, 8 injection needles and 4 cleansing swabs;
- 6 vials of powder for solution for injection and 6 ampoules of solvent for parenteral use;
- 12 vials of powder for solution for injection, 12 ampoules of solvent for parenteral use, 12 injection syringes, 24 injection needles and 12 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency
http://www.ema.europa.eu

**HOW TO SELF-INJECT PEGINTRON?**

The following instructions explain how to inject PegIntron yourself. Please read the instructions carefully and follow them step by step. Your doctor or his/her assistant will instruct you how to self-inject PegIntron. Do not attempt to inject yourself unless you are sure you understand the procedure and requirement of self-injection.

Preparation
Collect the necessary items before you begin:
- a vial of PegIntron powder for injection;
- an ampoule of solvent for PegIntron (water for injections);
- a 1 ml syringe;
- a long needle (for example 0.8 × 40 mm [21 gauge 1.5 inch]) to be used to add water for injections to the PegIntron powder vial;
- a short needle (for example 0.3 × 13 mm [30 gauge 0.5 inch]) for the subcutaneous injection;
- a cleansing swab.

Wash your hands carefully.

Reconstituting PegIntron powder for injection
Before reconstitution, PegIntron may appear either as a white, tablet-shaped solid that is whole or in pieces, or as a white powder.
Remove the protective cap from the PegIntron vial. Clean the rubber top of the vial with a cleansing swab. You can save the swab to clean the skin area where you will inject the dose. Remove the syringe from the wrapping. Do not touch the tip of the syringe. Take the long needle and place it firmly on to the tip of the syringe. Remove the needle guard without touching the needle and keep the syringe with the needle in your hand. Tap the top of the ampoule of solvent gently to make sure that all the liquid is at the bottom of the ampoule. Break off the top of the ampoule of solvent. Insert the needle in the ampoule of solvent and withdraw the total amount of solvent.

When the total amount of solvent is combined with the full amount of PegIntron powder, the solution will be at the correct concentration to measure your dose (i.e., the labelled amount is contained in 0.5 ml).

A small volume is lost during preparation of PegIntron for injection and when the dose is measured and injected. Therefore, each vial contains an excess amount of solvent and PegIntron powder to ensure delivery of the labelled dose in 0.5 ml of PegIntron, solution for injection.

To prepare the PegIntron solution, insert the needle through the rubber top of the PegIntron vial and gently place the needle tip against the glass wall of the vial without touching the cleaned top of the vial with your hands.
Inject the solvent **SLOWLY**, aiming the stream of liquid at the glass wall of the vial. It is best not to aim the stream directly at the white solid or powder, or to inject the liquid quickly, as this causes a greater amount of bubbles. The solution may appear cloudy or bubbly for a few minutes. This is to be expected and is not cause for concern.

To dissolve the entire contents, swirl the PegIntron vial with a gentle rotary motion leaving the needle and attached syringe in the vial. **Do not shake**, but gently turn the vial upside down until any powder at the top of the vial is dissolved. The contents should now be completely dissolved. Stand the vial upright and let any bubbles present in the solution rise to the top of the solution. Once the solution has settled and all bubbles have risen to the top of the solution, you should have a clear solution with a small ring of tiny bubbles around the top. Now you can withdraw your dose from the vial. Use this solution immediately. If it cannot be used immediately, the solution may be refrigerated for up to 24 hours.

Measuring the dose of PegIntron from the reconstituted powder for injection
Turn the vial and the syringe upside down in one hand. Be sure the tip of needle is in the PegIntron reconstituted solution. Your other hand will be free to move the plunger. Pull back on the plunger

slowly to draw just more than the dose prescribed by your doctor into the syringe.
Hold the syringe with the needle in the vial pointing up, remove the syringe from the long needle leaving the needle in the vial and without touching the tip of the syringe. Take the short needle and place it firmly on to the tip of the syringe. Remove the needle guard from the syringe needle and check for air bubbles in the syringe. If you see any bubbles, pull the plunger slightly back; tap the syringe gently, with the needle pointing upwards, until the bubbles disappear. Push up the plunger slowly back to the correct dose. Replace the needle guard and place the syringe with the needle on a flat surface.

Be sure the solution is at room temperature up to 25°C. If the solution is cold, warm the syringe between your palms. Inspect visually the reconstituted solution prior to administration: do not use if discolouration or particulate matter is present. You are now ready to inject the dose.

Injecting the solution
Select the injection site. The best sites for injection are tissues with a layer of fat between skin and muscle: thigh, outer surface of the upper arm (you may need the assistance of another person to use this site), abdomen (except the navel or waistline). If you are exceptionally thin, use only the thigh or outer surface of the arm for injection.
**Change your injection site each time.**

Cleanse and disinfect the skin where the injection is to be made. Wait for the area to dry. Remove the needle guard. With one hand, pinch a fold of loose skin. With your other hand, hold the syringe as you would a pencil. Insert the needle into the pinched skin at an angle of approximately 45°. After the needle is in, remove the hand used to pinch the skin and use it to hold the syringe barrel. Pull back the plunger very slightly with one hand. If blood comes into the syringe, the needle has entered a blood vessel. Do not inject into this site; withdraw the needle and repeat the procedure. Inject the solution by pushing the plunger all the way down gently.
Pull the needle straight out of the skin. Press the injection site with a small bandage or sterile gauze if necessary for several seconds. Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
The vial, ampoule and injection materials intended for single use must be discarded. Dispose of the syringe and needles safely in a closed container.

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 50 micrograms powder and solvent for solution for injection in pre-filled pen**
Peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre-filled pen and any unused solution contained in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each pre-filled pen contains 50 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection in a pre-filled pen.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 50 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

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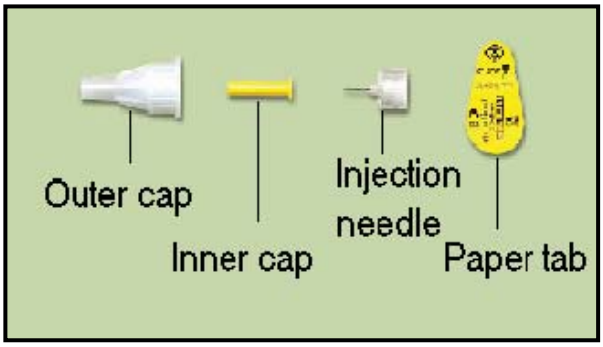
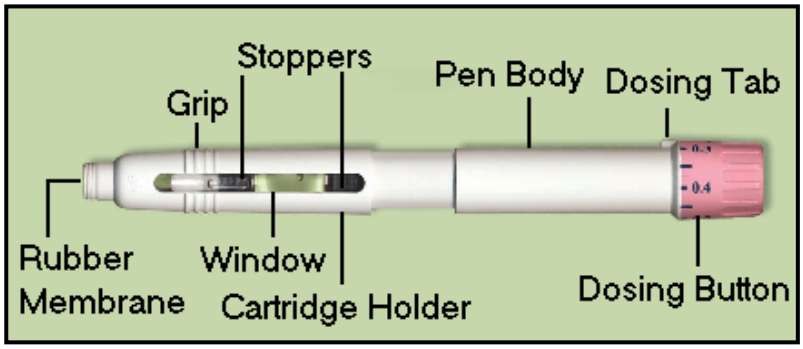
**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

## ANNEX TO THE PACKAGE LEAFLET

### How to use the PegIntron pre-filled pen




The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read all of the instructions carefully before attempting to use the pen and follow them step by step.**
Your doctor or his/her assistant will show you how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand everything fully.

The PegIntron pre-filled pen should be used by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the pack **only** for the PegIntron pre-filled pen. Make sure that the pen is at room temperature before you use it. Your doctor will have told you what dose you need to take for your treatment.

**Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.**

**Preparation:**

a. Find a clean, well-lit, non-slip flat working surface and get together all of the supplies you will need for the injection. All of the supplies you will need are in the PegIntron pack. The pack contains:
   - PegIntron pre-filled pen
   - one disposable injection needle
   - two cleansing swabs, and
   - dosing tray

b. The PegIntron pre-filled pen should be stored in the refrigerator, but take it out and allow it to come to room temperature before you use it. Before taking the PegIntron pre-filled pen out of its carton, check the expiration date printed on the carton. Do not use if the expiration date has passed.

c Take the PegIntron pre-filled pen out of the carton. Look in the window of the pen and make sure there is a white, to off-white tablet that is whole, or in pieces, or powdered. This is the PegIntron which will be mixed with liquid inside the pen before it is injected.

d. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important to keep your work area, your hands, and the injection site clean to lessen the risk of infection.

**Please follow the 4 major steps below to use the pen.**

**Step 1: Mix the medicine**

**Key points:**

**Before you mix the PegIntron, make sure it is at room temperature. It is important that you keep the PegIntron pre-filled pen upright (Dosing button down) (as shown in figure 1).**

- **Place the PegIntron pre-filled pen** upright in the holder of the tray provided in the pack (the dosing button will be on the **bottom**) on a hard, flat, non-slip surface. You may want to hold the pen using the grip.
- To mix the powder and the liquid, keep the PegIntron pre-filled pen upright in the dosing tray and **press the top half** of the pen **downward** toward the hard, flat, non-slip surface **until you hear the pen click.**

Once you have heard the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flush with the pen body.

- Wait for several seconds to let the powder dissolve.
- **Gently turn the pen upside down twice. DO NOT SHAKE THE PEN.**
- Keep the PegIntron pre-filled pen upright, with the dosing button down. Then, look through the pen window to see that the mixed PegIntron solution is competely dissolved. If there is still foam, wait until it settles.
- The solution should be clear and colourless before use. **Do not use** the solution if it is discoloured, not clear, or contains particles.
- Before attaching the needle, it is normal to see some small bubbles in the pre-filled pen window, near the top of the solution.
- Place the pen back into the holder in the tray with the dosing button on the bottom.

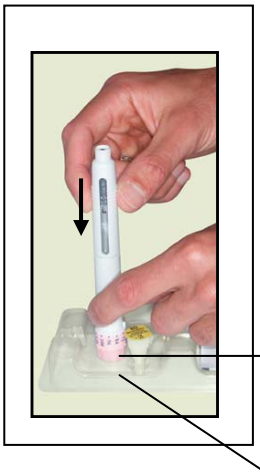



**Figure 1**

**<u>Step 2: Attach the needle</u>**

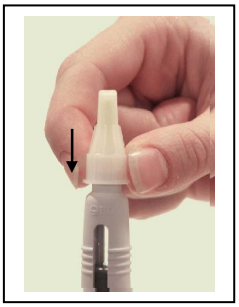


**Figure 2**

- Keeping the pen upright in the tray holder, wipe the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective **paper tab**, but **DO NOT** remove either the outer cap or the yellow inner cap from the injection needle.
- **Keeping the pen upright in the tray holder, FIRMLY** push the injection needle straight onto the pen rubber membrane (figure 2) and **screw it securely in place, in a clockwise direction**.

- Keep the PegIntron pre-filled pen **<u>UPRIGHT</u> (Dosing button down)** and keep both needle caps on until you are ready to inject.
- Screwing the needle into place, “primes” the needle and allows the extra liquid and air in the pen to be removed. **NOTE** : You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen. This is normal.
- Wait about 5 seconds for this process to finish.
- The dark stoppers **move up** and you will no longer see the fluid in the window once the needle is successfully primed (figure 3).

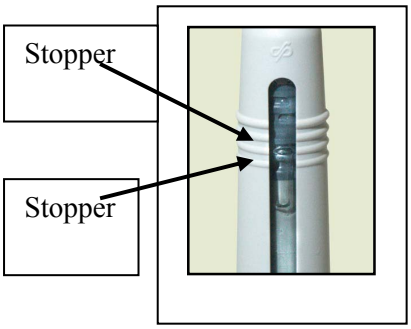



**Figure 3**

- Check through the window to be sure that the two stoppers are together. **If they are not together, do not use this pen because you may not be able to dial your dose (figure 3).**

**Step 3: Set the dose**


**Figure 4**

- Take the pen from the tray holder.
- Holding the pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without too much force being needed (figure 4).

**NOTE: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.**


**Figure 5**

- Turn the dosing button until your prescribed dose is in line with the dosing tab. The button should turn easily without too much force being needed (figure 5). If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go.

**NOTE**: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

- Carefully lay the pen down on a hard, flat, non-slip surface. DO NOT remove either of the needle caps and DO NOT push the dosing button in until you are ready to self-inject the PegIntron dose.

**Step 4: Inject the PegIntron solution**

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen). The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection. **You should use a different site each time you inject PegIntron to avoid soreness at any one site.** Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

- Clean the injection site skin with the second cleansing swab provided, and wait for the area to dry.

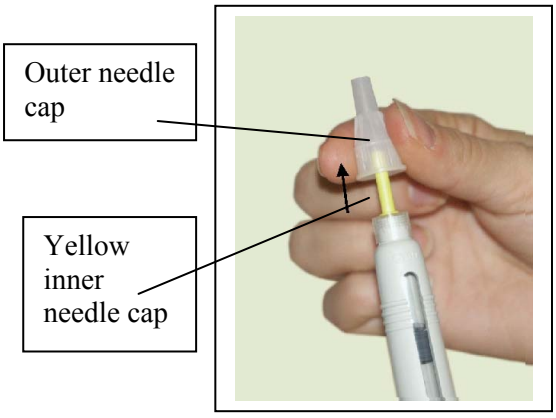



**Figure 6**

- Pull off the **outer needle cap (figure 6)**.
- There may be some liquid around the inner needle cap. Don't worry, this is normal. This liquid is not part of your dose, it is extra.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle. You are now ready to inject.

**Figure 7**

- **Hold the PegIntron pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button** (figure 7)**.**
- With your other hand, pinch a fold of loose skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Keep your thumb pressed down on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Gently press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

**After 2 hours, check the injection site for redness, swelling, or tenderness.**
**If you have a skin reaction and it doesn't clear up in a few days, contact your health care professional.**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 80 micrograms powder and solvent for solution for injection in pre-filled pen**
Peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre-filled pen and any unused solution contained in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each pre-filled pen contains 80 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection in a pre-filled pen.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 80 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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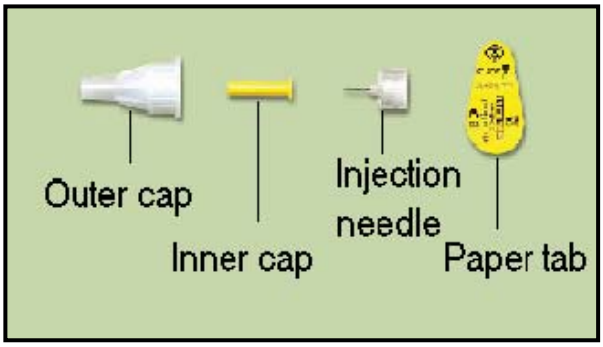
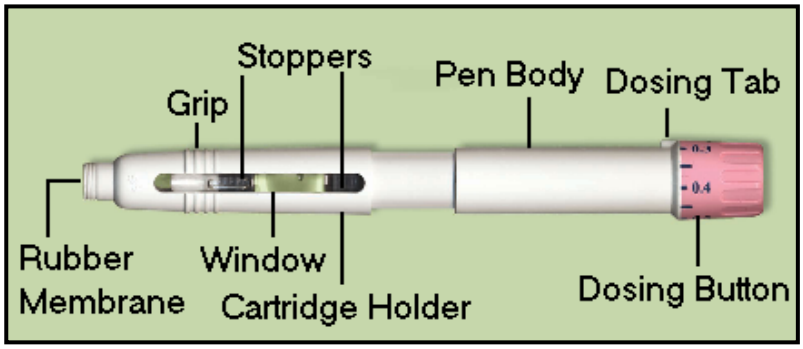
**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

## ANNEX TO THE PACKAGE LEAFLET

### How to use the PegIntron pre-filled pen




The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read all of the instructions carefully before attempting to use the pen and follow them step by step.**
Your doctor or his/her assistant will show you how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand everything fully.

The PegIntron pre-filled pen should be used by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the pack **only** for the PegIntron pre-filled pen. Make sure that the pen is at room temperature before you use it. Your doctor will have told you what dose you need to take for your treatment.

**Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.**

**Preparation:**

a. Find a clean, well-lit, non-slip flat working surface and get together all of the supplies you will need for the injection. All of the supplies you will need are in the PegIntron pack. The pack contains:
   - PegIntron pre-filled pen
   - one disposable injection needle
   - two cleansing swabs, and
   - dosing tray

b. The PegIntron pre-filled pen should be stored in the refrigerator, but take it out and allow it to come to room temperature before you use it. Before taking the PegIntron pre-filled pen out of its carton, check the expiration date printed on the carton. Do not use if the expiration date has passed.

c Take the PegIntron pre-filled pen out of the carton. Look in the window of the pen and make sure there is a white, to off-white tablet that is whole, or in pieces, or powdered. This is the PegIntron which will be mixed with liquid inside the pen before it is injected.

d. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important to keep your work area, your hands, and the injection site clean to lessen the risk of infection.

**Please follow the 4 major steps below to use the pen.**

**Step 1: Mix the medicine**

**Key points:**

**Before you mix the PegIntron, make sure it is at room temperature. It is important that you keep the PegIntron pre-filled pen upright (Dosing button down) (as shown in figure 1).**

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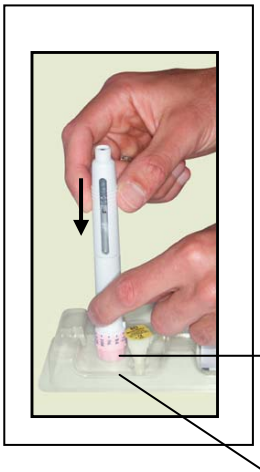


**Figure 1**

- **Place the PegIntron pre-filled pen** upright in the holder of the tray provided in the pack (the dosing button will be on the **bottom**) on a hard, flat, non-slip surface. You may want to hold the pen using the grip.
- To mix the powder and the liquid, keep the PegIntron pre-filled pen upright in the dosing tray and **press the top half** of the pen **downward** toward the hard, flat, non-slip surface **until you hear the pen click.**

Once you have heard the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flush with the pen body.

- Wait for several seconds to let the powder dissolve.
- **Gently turn the pen upside down twice. DO NOT SHAKE THE PEN.**
- Keep the PegIntron pre-filled pen upright, with the dosing button down. Then, look through the pen window to see that the mixed PegIntron solution is competely dissolved. If there is still foam, wait until it settles.
- The solution should be clear and colourless before use. **Do not use** the solution if it is discoloured, not clear, or contains particles.
- Before attaching the needle, it is normal to see some small bubbles in the pre-filled pen window, near the top of the solution.
- Place the pen back into the holder in the tray with the dosing button on the bottom.

**Step 2: Attach the needle**

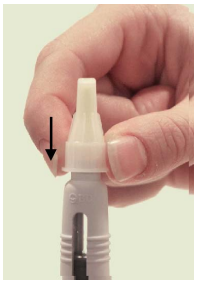

**Figure 2**

- Keeping the pen upright in the tray holder, wipe the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective **paper tab**, but **DO NOT** remove either the outer cap or the yellow inner cap from the injection needle.
- **Keeping the pen upright in the tray holder, FIRMLY** push the injection needle straight onto the pen rubber membrane (figure 2) and **screw it securely in place, in a clockwise direction**.

- Keep the PegIntron pre-filled pen **UPRIGHT (Dosing button down)** and keep both needle caps on until you are ready to inject.
- Screwing the needle into place, “primes” the needle and allows the extra liquid and air in the pen to be removed. **NOTE** : You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen. This is normal.
- Wait about 5 seconds for this process to finish.
- The dark stoppers **move up** and you will no longer see the fluid in the window once the needle is successfully primed (figure 3).

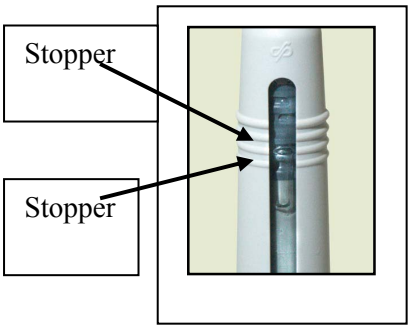


**Figure 3**

- Check through the window to be sure that the two stoppers are together. **If they are not together, do not use this pen because you may not be able to dial your dose (figure 3).**

**Step 3: Set the dose**


**Figure 4**

- Take the pen from the tray holder.
- Holding the pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without too much force being needed (figure 4).

**NOTE: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.**


**Figure 5**

- Turn the dosing button until your prescribed dose is in line with the dosing tab. The button should turn easily without too much force being needed (figure 5). If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go.

**NOTE**: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

- Carefully lay the pen down on a hard, flat, non-slip surface. DO NOT remove either of the needle caps and DO NOT push the dosing button in until you are ready to self-inject the PegIntron dose.

**Step 4: Inject the PegIntron solution**

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen). The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection. **You should use a different site each time you inject PegIntron to avoid soreness at any one site.** Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

- Clean the injection site skin with the second cleansing swab provided, and wait for the area to dry.

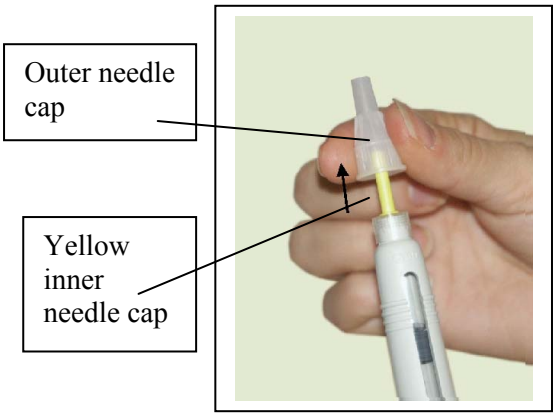


**Figure 6**

- Pull off the **outer needle cap (figure 6)**.
- There may be some liquid around the inner needle cap. Don't worry, this is normal. This liquid is not part of your dose, it is extra.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle. You are now ready to inject.

**Figure 7**

- **Hold the PegIntron pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button** (figure 7)**.**
- With your other hand, pinch a fold of loose skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Keep your thumb pressed down on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Gently press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

**After 2 hours, check the injection site for redness, swelling, or tenderness.**
**If you have a skin reaction and it doesn't clear up in a few days, contact your health care professional.**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 100 micrograms powder and solvent for solution for injection in pre-filled pen**
Peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*
- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre-filled pen and any unused solution contained in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each pre-filled pen contains 100 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection in a pre-filled pen.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 100 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

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SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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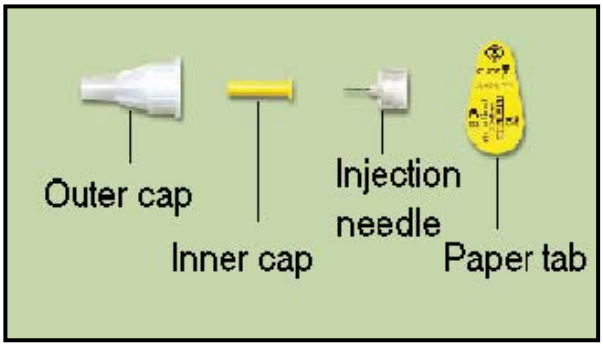
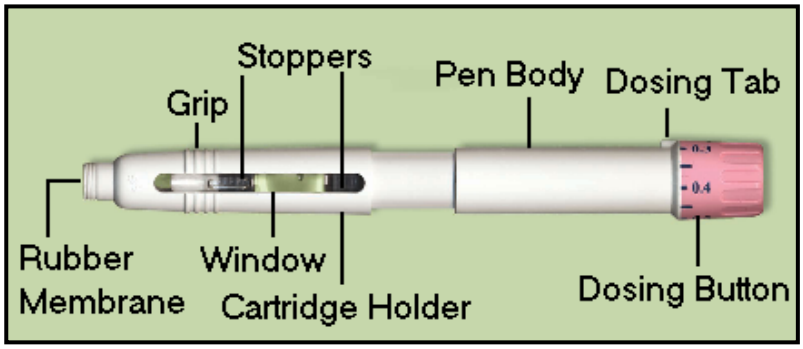
**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

## ANNEX TO THE PACKAGE LEAFLET

### How to use the PegIntron pre-filled pen




The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read all of the instructions carefully before attempting to use the pen and follow them step by step.**
Your doctor or his/her assistant will show you how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand everything fully.

The PegIntron pre-filled pen should be used by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the pack **only** for the PegIntron pre-filled pen. Make sure that the pen is at room temperature before you use it. Your doctor will have told you what dose you need to take for your treatment.

**Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.**

**Preparation:**

a. Find a clean, well-lit, non-slip flat working surface and get together all of the supplies you will need for the injection. All of the supplies you will need are in the PegIntron pack. The pack contains:
   - PegIntron pre-filled pen
   - one disposable injection needle
   - two cleansing swabs, and
   - dosing tray

b. The PegIntron pre-filled pen should be stored in the refrigerator, but take it out and allow it to come to room temperature before you use it. Before taking the PegIntron pre-filled pen out of its carton, check the expiration date printed on the carton. Do not use if the expiration date has passed.

c Take the PegIntron pre-filled pen out of the carton. Look in the window of the pen and make sure there is a white, to off-white tablet that is whole, or in pieces, or powdered. This is the PegIntron which will be mixed with liquid inside the pen before it is injected.

d. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important to keep your work area, your hands, and the injection site clean to lessen the risk of infection.

**Please follow the 4 major steps below to use the pen.**

**Step 1: Mix the medicine**

**Key points:**

**Before you mix the PegIntron, make sure it is at room temperature. It is important that you keep the PegIntron pre-filled pen upright (Dosing button down) (as shown in figure 1).**

•

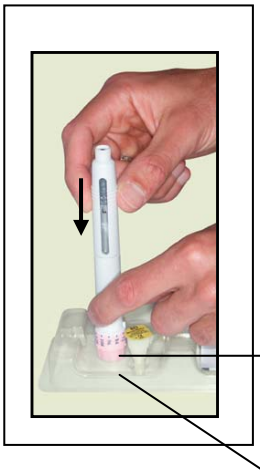



**Figure 1**

- **Place the PegIntron pre-filled pen** upright in the holder of the tray provided in the pack (the dosing button will be on the **bottom**) on a hard, flat, non-slip surface. You may want to hold the pen using the grip.
- To mix the powder and the liquid, keep the PegIntron pre-filled pen upright in the dosing tray and **press the top half** of the pen **downward** toward the hard, flat, non-slip surface **until you hear the pen click.**

Once you have heard the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flush with the pen body.

- Wait for several seconds to let the powder dissolve.
- **Gently turn the pen upside down twice. DO NOT SHAKE THE PEN.**
- Keep the PegIntron pre-filled pen upright, with the dosing button down. Then, look through the pen window to see that the mixed PegIntron solution is competely dissolved. If there is still foam, wait until it settles.
- The solution should be clear and colourless before use. **Do not use** the solution if it is discoloured, not clear, or contains particles.
- Before attaching the needle, it is normal to see some small bubbles in the pre-filled pen window, near the top of the solution.
- Place the pen back into the holder in the tray with the dosing button on the bottom.

**Step 2: Attach the needle**

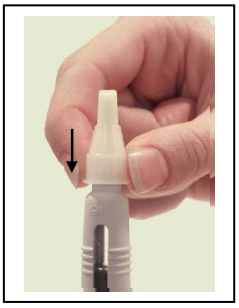


**Figure 2**

- Keeping the pen upright in the tray holder, wipe the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective **paper tab**, but **DO NOT** remove either the outer cap or the yellow inner cap from the injection needle.
- **Keeping the pen upright in the tray holder, FIRMLY** push the injection needle straight onto the pen rubber membrane (figure 2) and **screw it securely in place, in a clockwise direction**.

- Keep the PegIntron pre-filled pen **UPRIGHT (Dosing button down)** and keep both needle caps on until you are ready to inject.
- Screwing the needle into place, "primes" the needle and allows the extra liquid and air in the pen to be removed. **NOTE** : You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen. This is normal.
- Wait about 5 seconds for this process to finish.
- The dark stoppers **move up** and you will no longer see the fluid in the window once the needle is successfully primed (figure 3).

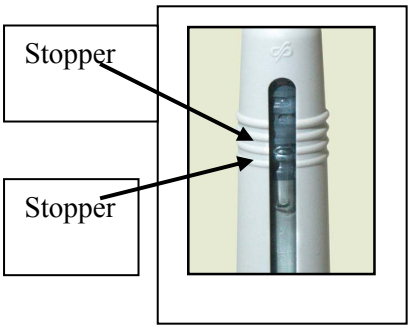



**Figure 3**

- Check through the window to be sure that the two stoppers are together. **If they are not together, do not use this pen because you may not be able to dial your dose (figure 3).**

**Step 3: Set the dose**


**Figure 4**

- Take the pen from the tray holder.
- Holding the pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without too much force being needed (figure 4).

**NOTE: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.**


**Figure 5**

- Turn the dosing button until your prescribed dose is in line with the dosing tab. The button should turn easily without too much force being needed (figure 5). If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go.

**NOTE**: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

- Carefully lay the pen down on a hard, flat, non-slip surface. DO NOT remove either of the needle caps and DO NOT push the dosing button in until you are ready to self-inject the PegIntron dose.

**Step 4: Inject the PegIntron solution**

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen). The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection. **You should use a different site each time you inject PegIntron to avoid soreness at any one site.** Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

- Clean the injection site skin with the second cleansing swab provided, and wait for the area to dry.

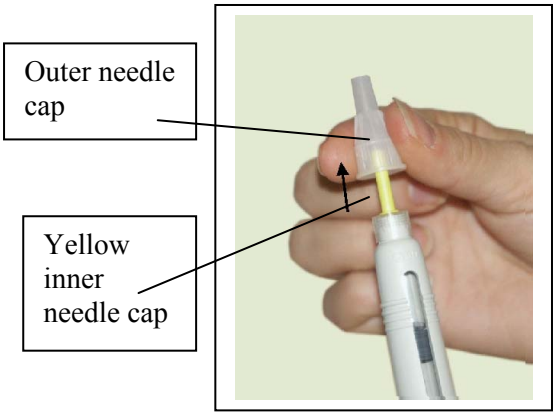



**Figure 6**

- Pull off the **outer needle cap (figure 6)**.
- There may be some liquid around the inner needle cap. Don't worry, this is normal. This liquid is not part of your dose, it is extra.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle. You are now ready to inject.

**Figure 7**

- **Hold the PegIntron pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button** (figure 7)**.**
- With your other hand, pinch a fold of loose skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Keep your thumb pressed down on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Gently press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

**After 2 hours, check the injection site for redness, swelling, or tenderness.**
**If you have a skin reaction and it doesn't clear up in a few days, contact your health care professional.**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 120 micrograms powder and solvent for solution for injection in pre-filled pen**
Peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*

- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**

- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**

Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>

Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre-filled pen and any unused solution contained in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each pre-filled pen contains 120 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection in a pre-filled pen.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 120 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
SP Labo N.V., Industriepark, 30, B-2220 Heist-op-den-Berg, Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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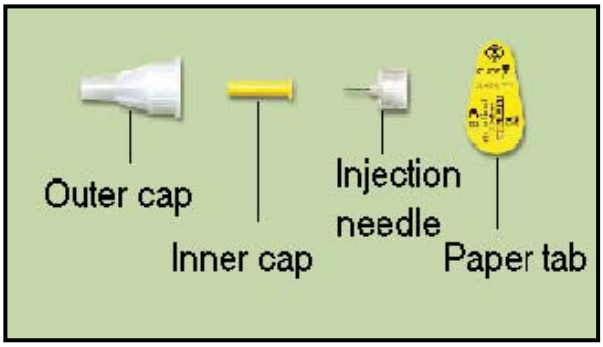
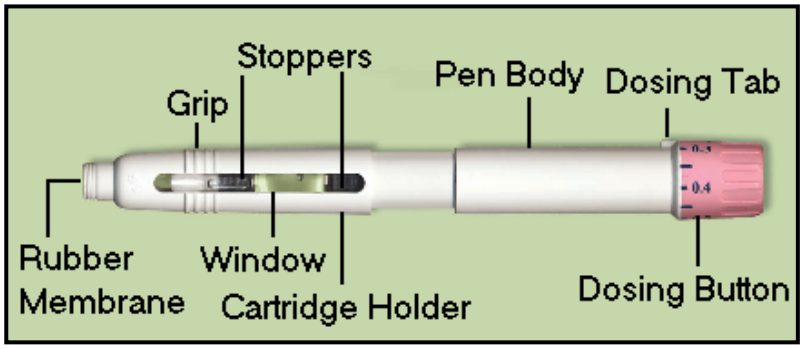
**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

## ANNEX TO THE PACKAGE LEAFLET

### How to use the PegIntron pre-filled pen




The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read all of the instructions carefully before attempting to use the pen and follow them step by step.**
Your doctor or his/her assistant will show you how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand everything fully.

The PegIntron pre-filled pen should be used by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the pack **only** for the PegIntron pre-filled pen. Make sure that the pen is at room temperature before you use it. Your doctor will have told you what dose you need to take for your treatment.

**Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.**

**Preparation:**

a. Find a clean, well-lit, non-slip flat working surface and get together all of the supplies you will need for the injection. All of the supplies you will need are in the PegIntron pack. The pack contains:
   - PegIntron pre-filled pen
   - one disposable injection needle
   - two cleansing swabs, and
   - dosing tray

b. The PegIntron pre-filled pen should be stored in the refrigerator, but take it out and allow it to come to room temperature before you use it. Before taking the PegIntron pre-filled pen out of its carton, check the expiration date printed on the carton. Do not use if the expiration date has passed.

c Take the PegIntron pre-filled pen out of the carton. Look in the window of the pen and make sure there is a white, to off-white tablet that is whole, or in pieces, or powdered. This is the PegIntron which will be mixed with liquid inside the pen before it is injected.

d. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important to keep your work area, your hands, and the injection site clean to lessen the risk of infection.

**Please follow the 4 major steps below to use the pen.**

**Step 1: Mix the medicine**

**Key points:**

**Before you mix the PegIntron, make sure it is at room temperature. It is important that you keep the PegIntron pre-filled pen upright (Dosing button down) (as shown in figure 1).**

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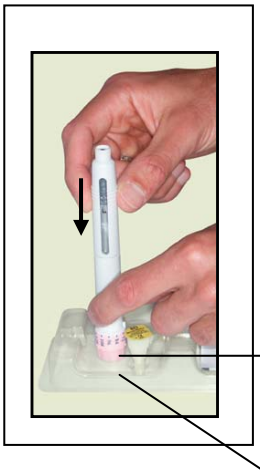


**Figure 1**

- **Place the PegIntron pre-filled pen** upright in the holder of the tray provided in the pack (the dosing button will be on the **bottom**) on a hard, flat, non-slip surface. You may want to hold the pen using the grip.
- To mix the powder and the liquid, keep the PegIntron pre-filled pen upright in the dosing tray and **press the top half** of the pen **downward** toward the hard, flat, non-slip surface **until you hear the pen click.**

Once you have heard the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flush with the pen body.

- Wait for several seconds to let the powder dissolve.
- **Gently turn the pen upside down twice. DO NOT SHAKE THE PEN.**
- Keep the PegIntron pre-filled pen upright, with the dosing button down. Then, look through the pen window to see that the mixed PegIntron solution is competely dissolved. If there is still foam, wait until it settles.
- The solution should be clear and colourless before use. **Do not use** the solution if it is discoloured, not clear, or contains particles.
- Before attaching the needle, it is normal to see some small bubbles in the pre-filled pen window, near the top of the solution.
- Place the pen back into the holder in the tray with the dosing button on the bottom.

**Step 2: Attach the needle**

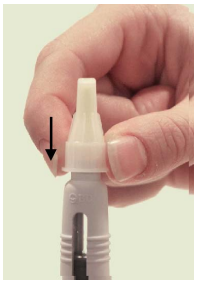

**Figure 2**

- Keeping the pen upright in the tray holder, wipe the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective **paper tab**, but **DO NOT** remove either the outer cap or the yellow inner cap from the injection needle.
- **Keeping the pen upright in the tray holder, FIRMLY** push the injection needle straight onto the pen rubber membrane (figure 2) and **screw it securely in place, in a clockwise direction**.

- Keep the PegIntron pre-filled pen **UPRIGHT (Dosing button down)** and keep both needle caps on until you are ready to inject.
- Screwing the needle into place, “primes” the needle and allows the extra liquid and air in the pen to be removed. **NOTE** : You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen. This is normal.
- Wait about 5 seconds for this process to finish.
- The dark stoppers **move up** and you will no longer see the fluid in the window once the needle is successfully primed (figure 3).

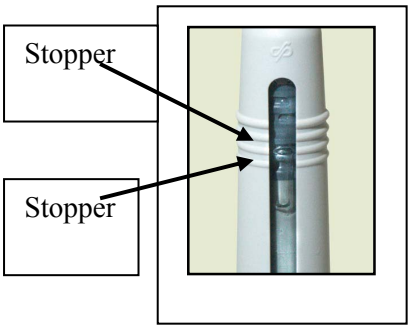


**Figure 3**

- Check through the window to be sure that the two stoppers are together. **If they are not together, do not use this pen because you may not be able to dial your dose (figure 3).**

**Step 3: Set the dose**


**Figure 4**

- Take the pen from the tray holder.
- Holding the pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without too much force being needed (figure 4).

**NOTE: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.**


**Figure 5**

- Turn the dosing button until your prescribed dose is in line with the dosing tab. The button should turn easily without too much force being needed (figure 5). If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go.

**NOTE**: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

- Carefully lay the pen down on a hard, flat, non-slip surface. DO NOT remove either of the needle caps and DO NOT push the dosing button in until you are ready to self-inject the PegIntron dose.

**Step 4: Inject the PegIntron solution**

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen). The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection. **You should use a different site each time you inject PegIntron to avoid soreness at any one site.** Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

- Clean the injection site skin with the second cleansing swab provided, and wait for the area to dry.

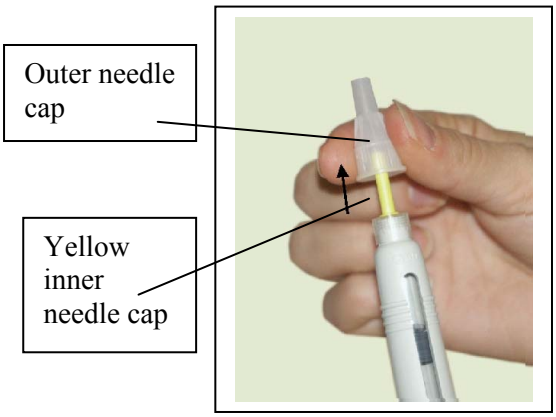


**Figure 6**

- Pull off the **outer needle cap (figure 6)**.
- There may be some liquid around the inner needle cap. Don't worry, this is normal. This liquid is not part of your dose, it is extra.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle. You are now ready to inject.

**Figure 7**

- **Hold the PegIntron pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button** (figure 7)**.**
- With your other hand, pinch a fold of loose skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Keep your thumb pressed down on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Gently press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

**After 2 hours, check the injection site for redness, swelling, or tenderness.**
**If you have a skin reaction and it doesn't clear up in a few days, contact your health care professional.**

**PACKAGE LEAFLET: INFORMATION FOR THE USER**

**PegIntron 150 micrograms powder and solvent for solution for injection in pre-filled pen**
Peginterferon alfa-2b

**Read all of this leaflet carefully before you start using this medicine.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet**:

1. What PegIntron is and what it is used for
2. Before you use PegIntron
3. How to use PegIntron
4. Possible side effects
5. Storing PegIntron
6. Further information


## 1. WHAT PEGINTRON IS AND WHAT IT IS USED FOR

Interferons modify the response of the body's immune system to help fight infections and severe diseases. PegIntron, which contains an interferon, is used in adults for the treatment of chronic hepatitis C, a viral infection of the liver.

PegIntron is best used for this treatment in combination with ribavirin.

*Adult patients*
This combination is indicated in first-time users, including in first-time users co-infected with clinically stable HIV. This combination is also indicated in relapse patients and patients who have not responded previously to interferon alpha (pegylated or non-pegylated) and ribavirin combination therapy or interferon alpha monotherapy.

PegIntron is used alone in case of intolerance or contraindication to ribavirin.

*Children and adolescents*
PegIntron is used in combination with ribavirin in children 3 years of age and older and adolescents who have previously untreated chronic hepatitis C.

## 2. BEFORE YOU USE PEGINTRON

**Do not use PegIntron**
- If you are allergic (hypersensitive) to peginterferon alfa-2b or any of the other ingredients of PegIntron.
- If you are allergic (hypersensitive) to any interferon.
- If you have had severe heart problems, or if you have heart disease that has not been well controlled during the past 6 months.
- If you have severe medical conditions that leave you very weak.
- If you have autoimmune hepatitis or any other problem with your immune system; if you are taking medicine that suppresses your immune system (your immune system protects you against infection and some diseases).
- If you have advanced, uncontrolled liver disease (other than hepatitis C).
- If you have thyroid disease that is not well controlled with medicines.

- If you have a condition that causes convulsions (seizures, or “fits”).

*Children and adolescents*
- If you have had serious nervous or mental problems, such as severe depression or thoughts of suicide.

**Take special care with PegIntron**
- If you develop symptoms of a severe allergic reaction (such as difficulty in breathing, wheezing, or hives) while on this medication, seek medical help immediately.
- If you ever had a heart attack or a heart problem.
- If you have ever been treated for depression or any other nervous or mental disorder.
- If you have kidney disease, your doctor may prescribe a lower than usual dose and monitor your kidney blood values regularly during treatment. If you have a kidney disease and you are using PegIntron in combination with medicines containing ribavirin, your doctor should monitor you more carefully for a decrease in red blood cell count.
- If you have had a problem with your liver (other than hepatitis C).
- If you develop symptoms associated with a cold or other respiratory infection, such as fever, cough, or any difficulty in breathing, tell your doctor.
- If you are diabetic, your doctor may ask you to have an eye examination.
- If you have had any serious illness affecting your breathing or your blood.
- If you have psoriasis, it may become worse while you are using PegIntron.
- If you are planning to become pregnant, discuss this with your doctor before starting to use PegIntron.
- If you are also being treated for HIV (see **Using other medicines)**.
- If you have had a severe nervous or mental disorder.
  The use of PegIntron in children and adolescents with existence of or history of severe psychiatric conditions is contraindicated (see **Do not use PegIntron**).
- If you ever had depression or develop symptoms associated with depression (e.g. feelings of sadness, dejection, etc) while on treatment with PegIntron (see section 4).
- If you have received an organ transplant, either kidney or liver, interferon treatment may increase the risk of rejection. Be sure to discuss this with your doctor.

PegIntron is not recommended for use in patients under the age of 3 years.

Dental and gum disorders, which may lead to loss of teeth, have been reported in patients receiving PegIntron and ribavirin combination therapy. In addition, dry mouth could have a damaging effect on teeth and membranes of the mouth during long-term treatment with the combination of PegIntron with ribavirin. You should brush your teeth thoroughly twice daily and have regular dental examinations. In addition some patients may experience vomiting. If you have this reaction, be sure to rinse your mouth thoroughly afterwards.

**While being treated with PegIntron**
Your doctor may want you to drink extra fluids to help prevent low blood pressure.

**Using other medicines**
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

<u>Patients who also have HIV infection</u>
Lactic acidosis and worsening liver function are side effects associated with Highly Active Anti-Retroviral Therapy (HAART), an HIV treatment. If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis and of liver failure. Your doctor will monitor you for signs and symptoms of these conditions. (Please be sure to read the ribavirin Patient Leaflet also). Additionally, patients treated with PegIntron and ribavirin combination therapy and zidovudine could be at increased risk of developing anaemia (low number of red blood cells). If you are also being treated for Human Immunodeficiency Virus (HIV) infection (AIDS) with zidovudine or stavudine, it is not certain if ribavirin will change the way these medicines work. Therefore, your

blood will be checked regularly to be sure that the HIV infection is not getting worse. If it gets worse, your doctor will decide whether or not your ribavirin treatment needs to be changed.
Co-administration of ribavirin and didanosine and/or stavudine is not recommended due to the risk of lactic acidosis (a build-up of lactic acid in the body) and pancreatitis.

**Pregnancy and breast-feeding**
Ask your doctor or pharmacist for advice before taking any medicine. In studies in pregnant animals, interferons have sometimes caused miscarriage. The effect on human pregnancy is not known. In combination therapy with ribavirin, ribavirin can be very damaging to an unborn baby, thus both female and male patients must take special precautions in their sexual activity if there is any chance for pregnancy to occur:
- if you are a **girl** or a **woman** of childbearing age, you must have a negative pregnancy test before treatment, each month during treatment, and for the 4 months after treatment is stopped. You and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 4 months after stopping treatment. This can be discussed with your doctor.
- if you are a **man** who is taking ribavirin, do not have sex with a pregnant woman unless you use a condom. This will lessen the chance for ribavirin to be left in the woman's body. If your female partner is not pregnant now but is of childbearing age, she must be tested for pregnancy each month during treatment and for the 7 months after treatment has stopped. This can be discussed with your doctor. If you are a male patient, you and your partner must each use an effective contraceptive during the time you are taking ribavirin and for 7 months after stopping treatment. This can be discussed with your doctor.

It is not known whether this medicine is present in human milk. Therefore, do not breast-feed an infant if you are taking PegIntron. In combination therapy with ribavirin, take notice of the respective informing texts of ribavirin containing medicines.

**Driving and using machines**
Do not drive or operate any tools or machines if you feel tired, sleepy or confused while taking PegIntron.

**Important information about some of the ingredients of PegIntron**
This medicine contains sucrose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
This medicine contains less than 1 mmol sodium (23 mg) per 0.7 ml, i.e., essentially "sodium-free".

## 3. HOW TO USE PEGINTRON

Your doctor has prescribed PegIntron specifically for you and your current condition; do not share this medicine with anyone else.

Your doctor has determined your dose of PegIntron based on your weight. If necessary, the dose may be changed during treatment.

Combination treatment with ribavirin
- *Adults:*
PegIntron, when given with ribavirin capsules, is usually given at a dose of 1.5 microgram/kg once a week.

Ribavirin capsules are taken every day, morning and evening with food. The number of ribavirin capsules you take depends on your weight.
- If you weigh less than 65 kg, take 2 capsules in the morning and 2 in the evening (total of 800 mg each day).
- If you weigh between 65 and 80 kg, take 2 capsules in the morning and 3 in the evening (total of 1,000 mg each day).

- If you weigh between 81 and 105 kg, take 3 capsules in the morning and 3 in the evening (total of 1,200 mg each day).
- If you weigh more than 105 kg, take 3 capsules in the morning and 4 in the evening (total of 1,400 mg each day).

However, your doctor may modify your dose of either PegIntron or ribavirin. Follow what your doctor directs for you to do during your treatment.

In first-time users, the combination treatment is continued for 3 to 6 months, and sometimes for one year depending on your doctor's judgement. Take notice of the respective informing texts of ribavirin containing medicines.
For HCV/HIV co-infected patients, the duration of treatment is 48 weeks.
In patients who have not responded previously or relapsed, the treatment should continue for one year (contingent upon the response after the first 12 weeks of therapy).

- *Children 3 years of age and older and adolescents:*
Dosing for paediatric patients is determined by body surface area for PegIntron and by body weight for ribavirin. The recommended dose of PegIntron is 60 μg/$m^2$/week subcutaneously in combination with 15 mg/kg/day of ribavirin orally in two divided doses with food. The duration of treatment is up to 1 year based on your doctor's judgement.

PegIntron alone - Adults
PegIntron, when given alone, is usually given at a dose of 0.5 or 1.0 microgram/kg once a week, for at least 6 months, and possibly for 1 year. If you have kidney disease, your dose may be lower, depending upon your kidney function.
PegIntron alone was not studied in HCV/HIV co-infected patients.

All patients
If you are injecting PegIntron yourself, please be sure that the dose that has been prescribed for you is clearly provided on the package of medicine you receive.

If you have the impression that the effect of PegIntron is too strong or too weak, talk to your doctor or pharmacist.

PegIntron is intended for subcutaneous use. This means that it is injected through a short injection needle into the fatty tissue just under your skin. If you are injecting this medicine yourself, you will be instructed how to prepare and give the injection. Detailed instructions for subcutaneous administration are provided with this leaflet (see How to use the PegIntron pre-filled pen).

Prepare the dose just before you intend to inject it and use it immediately. Look carefully at the reconstituted solution prior to administration. Do not use if there is discolouration of the reconstituted solution or if particulate matter is present. PegIntron is intended for single use only. Thus, after you give yourself the injection, discard the PegIntron pre-filled pen with any solution that is left in it.

Inject PegIntron once each week on the same day. Injecting it at the same time of day each week will help you not to forget to take it.

Always use PegIntron exactly as your doctor told you. Do not exceed the recommended dose, and take it for as long as prescribed.

**If you use more PegIntron than you should**
Tell your doctor or healthcare professional as soon as possible.

**If you forget to take PegIntron**
If you are self-administering treatment, or if you are the caregiver of a child taking PegIntron in combination with ribavirin, take/administer the dose as soon as you remember, then continue your treatment as usual.

Do not take a double dose to make up for a forgotten dose. Contact your doctor or pharmacist if needed.

## 4. POSSIBLE SIDE EFFECTS

Like all medicines, PegIntron can cause side effects, although not everybody gets them. Although not all of these side effects may occur, they may need medical attention if they do.

**Psychiatric and central nervous system:**
Some people get depressed when taking PegIntron alone or in combination treatment with ribavirin, and in some cases people had thoughts about threatening the life of others, suicidal thoughts or aggressive behaviour (sometimes directed against others). Some patients have actually committed suicide. Be sure to seek emergency care if you notice that you are becoming depressed or have suicidal thoughts or change in your behaviour. You may want to consider asking a family member or close friend to help you stay alert to signs of depression or changes in your behaviour.

*Children and adolescents* are particularly prone to develop depression when being treated with PegIntron and ribavirin. Immediately contact the doctor or seek emergency treatment if they display any unusual behavioural symptoms, feel depressed, or feel they want to harm themselves or others.

**Growth and development (children and adolescents):**
With up to one year of treatment with PegIntron in combination with ribavirin, some children and adolescents did not grow or gain weight as much as expected. Some children did not reach their projected height within 1-5 years after completing treatment.

Check with your doctor immediately if any of the following side effects occur: chest pain; changes in the way your heart beats; breathing problems (including shortness of breath), confusion; feeling depressed, wanting to harm yourself, hallucinations, numbness or tingling feeling; dizziness, convulsion ("fit"); trouble sleeping, thinking or concentrating; difficulty remaining alert, severe stomach pain or cramps; blood or clots in stool (or black, tarry stool); fever or chills beginning after a few weeks of treatment, pain in your lower back or side; difficulty or inability to pass urine, painful or inflamed muscles (sometimes severe); problems with your eyes or your eyesight or hearing; severe or painful reddening of your skin or mucous membrane, severe bleeding from your nose. Your doctor will test your blood to ensure that your white blood cell (cells that fight infection) and red blood cell (cells that carry oxygen) counts, platelets (blood clotting cells) and other laboratory values are at acceptable levels.

Other side effects that have been reported in adults with the combination of PegIntron and ribavirin capsules include:

*Very common (greater than or equal to 1 in every 10 patients):*
Irritation or redness (and rarely, skin damage) at the site of injection, headache, tired feeling, shaking chills, fever, flu-like symptoms, weakness, loss of weight, nausea, loss of appetite, diarrhoea or loose stools, stomach pain, vomiting, muscle aches, pain in joints and muscles, feeling depressed, irritability, trouble falling asleep or staying asleep, feeling anxious or nervous, difficulty concentrating, mood swings, hair loss, itching, dry skin, sore throat, coughing, difficult breathing, dizziness, virus infection, rash, and dry mouth.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Increased sweating, chest pain, pain on the right side around your ribs, numbness, pain or tingling feeling, change in thyroid gland activity (which may make you feel tired or, less commonly, energetic), stomach upset, rapid heart rate, agitation, nervousness, difficult or irregular menstrual period.

Less common are pain at the place of injection, flushing, low or high blood pressure, dry or teary eyes, redness of skin or skin disorders, psoriasis, hives, nail disorder, feeling unwell, feeling faint, poor coordination, confusion, increased or decreased sensitivity to touch, tense muscles, limb pain, arthritis, bruising, loss of interest in activities including sex, erectile problem, sexual problem, unusual dreams,

shaky hands, vertigo (spinning feeling), increased appetite, heartburn, intestinal gas (flatus), constipation, bloating, hemorrhoids, red or bleeding gums, redness or sores in mouth, burning sensation on tongue, change in taste, tooth problem, changes in hearing or ringing in ears, thirst, changed behaviour or aggressive behaviour (sometimes directed against others), feeling sleepy, cold sores, fungal or bacterial infections, irritation of prostate gland, increased need to pass urine, ear or respiratory infections, sinusitis, stuffy or runny nose, abnormal hair texture, sensitivity to sunlight, migraine headache, eye pain or infection, blurred vision, puffy face, puffy hands or feet, enlarged liver, problem affecting ovary or vagina, pain in breast, sore throat, difficulty in speaking and swollen glands.

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Suicide.

The following side effects have been reported with PegIntron or PegIntron in combination with ribavirin:

*Uncommon (at least 1 in every 1,000 patients, but less than 1 in every 100 patients):*
Hypersensitivity reaction to the medication, panic attack, heart attack, inflammation of pancreas, pain in bone, and diabetes mellitus.

*Rare (at least 1 in every 10,000 patients, but less than 1 in every 1,000 patients):*
Diabetic ketoacidosis (medical emergency due to build-up of ketone bodies in the blood as a result of out-of-control diabetes), congestive heart failure, abnormal heart rhythm, pericarditis (inflammation of the lining of the heart), inflammation and degeneration of muscle tissue and peripheral nerves, kidney problems, seizures and bipolar disorders (mood disorders characterized by alternating episodes of sadness and excitement). Sarcoidosis (a disease characterised by persistent fever, weight loss, joint pain and swelling, skin lesions and swollen glands) has been reported.

*Very rare (less than 1 in every 10,000 patients):*
Loss of consciousness has occurred very rarely with alpha interferons, mostly in elderly patients treated at high doses. Cases of stroke (cerebrovascular events) have been reported. Check with your doctor immediately if you have any of these symptoms or any other symptoms that are troubling.

Very rarely, PegIntron alone or in combination with ribavirin may cause aplastic anaemia. Pure red cell aplasia, a condition where the body stopped or reduced the production of red blood cells, has been reported. This causes severe anaemia, symptoms of which would include unusual tiredness and a lack of energy.

Additionally, the following events have been reported with PegIntron: facial palsy (weakness and slumping on one side to the face) and severe allergic reactions such as angioedema (an allergic skin disease characterized by patches of circumscribed swelling involving the skin and its subcutaneous layers, the mucous membranes, and sometimes the internal organs), toxic epidermal necrolysis/Stevens Johnson Syndrome/erythema multiforme (a spectrum of rashes with varying degree of severity including death which may be associated with blisters in the mouth, nose, eyes and other mucosal membranes and sloughing of the affected area of the skin), mania (excessive or unreasonable enthusiasm), pericardial effusion (a fluid collection that develops between the pericardium (the lining of the heart) and the heart itself).

Additionally, Vogt-Koyanagi-Harada syndrome (an autoimmune inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord), thoughts about threatening the life of others, has been reported with PegIntron use.

When PegIntron is used alone, some of these effects are less likely to occur, and some have not occurred at all.

If you are receiving HAART, the addition of PegIntron and ribavirin may increase your risk of lactic acidosis, liver failure, and development of blood abnormalities (reduction in number of red blood cells

which carry oxygen, certain white blood cells that fight infection, and blood clotting cells called platelets).

The following other side effects (not listed above) have occurred with the combination of PegIntron and ribavirin capsules (adults) in HCV/HIV co-infected patients receiving HAART: oral candidiasis (oral thrush), defective metabolism of fat, CD4 lymphocytes decreased, appetite decreased, back pain, hepatitis, limb pain, and various laboratory blood values abnormalities.

The following effects have occurred with the combination of PegIntron/ribavirin in children and adolescents:

*Very common (greater than or equal to 1 in every 10 patients):*
Loss of appetite, dizziness, headache, vomiting, nausea, stomach pain, hair loss, dry skin, pain in joints and muscles, redness at the site of injection, feeling irritable, tired feeling, feeling unwell, pain, chills, fever, flu-like symptoms, weakness, decreased weight, decreases in red blood cells that may cause fatigue, shortness of breath, dizziness.

*Common (at least 1 in every 100 patients, but less than 1 in every 10 patients):*
Fungal infection, common cold, cold sores, pharyngitis (sore throat), sinusitis, ear infection, decrease in blood clotting cells called platelets, that may result in easy bruising and spontaneous bleeding, swollen glands (swollen lymph nodes), aggressive behaviour, agitation, anger, mood changes, nervousness or restlessness, depression, feeling anxious, trouble falling asleep or staying asleep, emotional instability, poor quality sleep, feeling sleepy, disturbance in attention, changes in taste, fainting, eye pain, palpitations (pounding heart beat), rapid heart rate, flushing, coughing, nosebleed, throat pain, sores in mouth, scaling lips and clefts in the corners of the mouth, diarrhoea, stomach upset, oral pain, rash, redness of skin, itching, eczema (inflamed, red, itchy and dryness of the skin with possible oozing lesions), acne, back pain, muscle and bone pain, limb pain, feeling cold, dryness, pain, rash, irritation or itching at the site of injection, blood thyroid tests abnormalities, decrease in thyroid gland activity, which may make you feel tired, depressed, increase your sensitivity to cold and other symptoms.

*Uncommon (at least 1 in every 1000 patients, but less than 1 in every 100 patients):*
Itchy anal area (pinworms or ascarids), redness, swelling, pain of skin, shingles, difficult breathing, painful or difficult urination, urinary frequency, inflammation of the lining membrane of the stomach and the intestines, abnormal behaviour, emotional disorder, fear, nightmare, tremor, decreased sensitivity to touch, numbness or tingling feeling, pain radiating along the course of one or more nerves, drowsiness, bleeding of the mucous membrane that lines the inner surface of the eyelids, itchy eyes, eye pain, blurred vision, intolerance to light, low blood pressure, paleness, nasal discomfort, runny nose, wheezing, inflamed gums, enlarged liver, skin sensitive to sunlight, rash with raised spotted lesions, skin discolouration, peeling of skin, shortening of muscle tissue, muscle twitching, the presence of excess protein in the urine, painful menstruation, chest pain or discomfort, facial pain, bruising.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

## 5. HOW TO STORE PEGINTRON

Keep out of the reach and sight of children.

Do not use PegIntron after the expiry date which is stated on the carton.

Store in a refrigerator (2°C - 8°C). Do not freeze.

After reconstitution, use the reconstituted solution immediately or within 24 hours when stored in a refrigerator (2°C - 8°C).

Do not use PegIntron if you notice discolouration of the powder.
The reconstituted solution should be clear and colourless. Do not use if discolouration or particulate matter is present. After administering the dose, discard the PegIntron pre-filled pen and any unused solution contained in it.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

## 6. FURTHER INFORMATION

**What PegIntron contains**

- The active substance is peginterferon alfa-2b. Each pre-filled pen contains 150 micrograms of peginterferon alfa-2b in 0.5 ml of solution when reconstituted as recommended.
- The other ingredients are:
  Powder: disodium phosphate, anhydrous, sodium dihydrogen phosphate dihydrate, sucrose and polysorbate 80;
  Solvent: water for injections.

**What PegIntron looks like and contents of the pack**

PegIntron is a powder and solvent for solution for injection in a pre-filled pen.
The white powder and the clear and colourless solvent are both contained in a two-chamber glass cartridge assembled into a single use pre-filled pen.

PegIntron 150 micrograms is available in different pack sizes:
- 1 pen containing powder and solvent for solution for injection, 1 injection needle and 2 cleansing swabs;
- 4 pens containing powder and solvent for solution for injection, 4 injection needles and 8 cleansing swabs;
- 6 pens containing powder and solvent for solution for injection, 6 injection needles and 12 cleansing swabs;
- 12 pens containing powder and solvent for solution for injection, 12 injection needles and 24 cleansing swabs.

Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
SP Europe, 73, rue de Stalle, B-1180 Bruxelles, Belgium

**Manufacturer**
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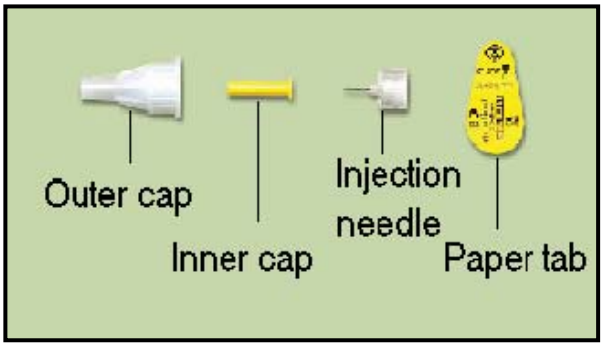
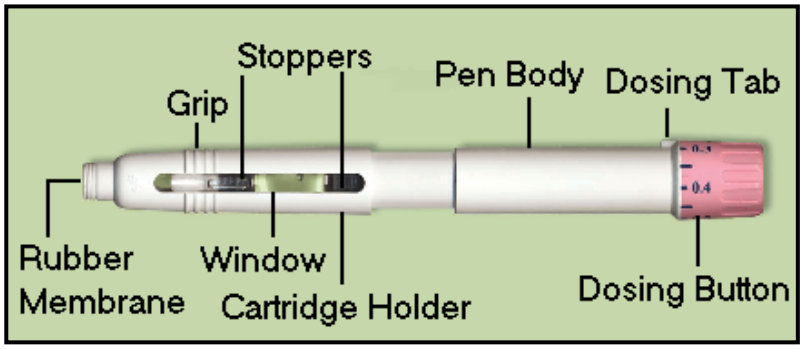
**This leaflet was last approved in**

Detailed information on this medicine is available on the web-site of the European Medicines Agency http://www.ema.europa.eu

## ANNEX TO THE PACKAGE LEAFLET

### How to use the PegIntron pre-filled pen




The following instructions explain how to inject yourself with the single use PegIntron pre-filled pen. **Please read all of the instructions carefully before attempting to use the pen and follow them step by step.**
Your doctor or his/her assistant will show you how to self-inject with the PegIntron pre-filled pen. Do not attempt to inject yourself unless you are sure you understand everything fully.

The PegIntron pre-filled pen should be used by one person only and must not be shared. Use the injection needle and cleansing swabs provided in the pack **only** for the PegIntron pre-filled pen. Make sure that the pen is at room temperature before you use it. Your doctor will have told you what dose you need to take for your treatment.

**Note: The colour of the dosing button is different for each strength of the PegIntron pre-filled pen.**

**Preparation:**

a. Find a clean, well-lit, non-slip flat working surface and get together all of the supplies you will need for the injection. All of the supplies you will need are in the PegIntron pack. The pack contains:
   - PegIntron pre-filled pen
   - one disposable injection needle
   - two cleansing swabs, and
   - dosing tray

b. The PegIntron pre-filled pen should be stored in the refrigerator, but take it out and allow it to come to room temperature before you use it. Before taking the PegIntron pre-filled pen out of its carton, check the expiration date printed on the carton. Do not use if the expiration date has passed.

c Take the PegIntron pre-filled pen out of the carton. Look in the window of the pen and make sure there is a white, to off-white tablet that is whole, or in pieces, or powdered. This is the PegIntron which will be mixed with liquid inside the pen before it is injected.

d. Wash your hands thoroughly with soap and water, rinse, and towel dry. It is important to keep your work area, your hands, and the injection site clean to lessen the risk of infection.

**Please follow the 4 major steps below to use the pen.**

**Step 1: Mix the medicine**

**Key points:**

**Before you mix the PegIntron, make sure it is at room temperature. It is important that you keep the PegIntron pre-filled pen upright (Dosing button down) (as shown in figure 1).**

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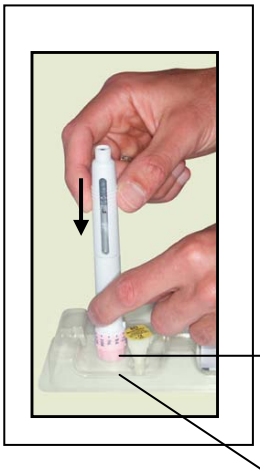


**Figure 1**

- **Place the PegIntron pre-filled pen** upright in the holder of the tray provided in the pack (the dosing button will be on the **bottom**) on a hard, flat, non-slip surface. You may want to hold the pen using the grip.
- To mix the powder and the liquid, keep the PegIntron pre-filled pen upright in the dosing tray and **press the top half** of the pen **downward** toward the hard, flat, non-slip surface **until you hear the pen click.**

Once you have heard the click, you will notice in the window that both dark stoppers are now touching. The dosing button should be flush with the pen body.

- Wait for several seconds to let the powder dissolve.
- **Gently turn the pen upside down twice. DO NOT SHAKE THE PEN.**
- Keep the PegIntron pre-filled pen upright, with the dosing button down. Then, look through the pen window to see that the mixed PegIntron solution is competely dissolved. If there is still foam, wait until it settles.
- The solution should be clear and colourless before use. **Do not use** the solution if it is discoloured, not clear, or contains particles.
- Before attaching the needle, it is normal to see some small bubbles in the pre-filled pen window, near the top of the solution.
- Place the pen back into the holder in the tray with the dosing button on the bottom.

**Step 2: Attach the needle**

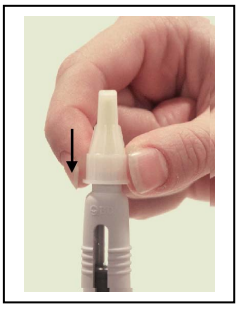

**Figure 2**

- Keeping the pen upright in the tray holder, wipe the rubber membrane of the PegIntron pre-filled pen with one cleansing swab.
- Take the injection needle provided in the tray and remove its protective **paper tab**, but **DO NOT** remove either the outer cap or the yellow inner cap from the injection needle.
- **Keeping the pen upright in the tray holder, FIRMLY** push the injection needle straight onto the pen rubber membrane (figure 2) and **screw it securely in place, in a clockwise direction**.

- Keep the PegIntron pre-filled pen **UPRIGHT (Dosing button down)** and keep both needle caps on until you are ready to inject.
- Screwing the needle into place, “primes” the needle and allows the extra liquid and air in the pen to be removed. **NOTE** : You may see some liquid trickle out from under the cap, as the air has been expelled out of the pen. This is normal.
- Wait about 5 seconds for this process to finish.
- The dark stoppers **move up** and you will no longer see the fluid in the window once the needle is successfully primed (figure 3).

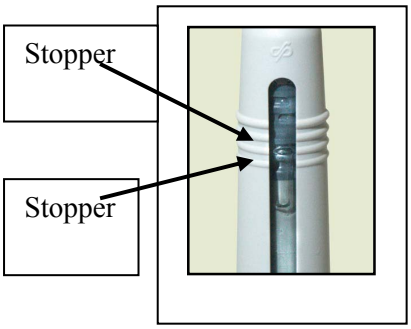


**Figure 3**

- Check through the window to be sure that the two stoppers are together. **If they are not together, do not use this pen because you may not be able to dial your dose (figure 3).**

**Step 3: Set the dose**


**Figure 4**

- Take the pen from the tray holder.
- Holding the pen firmly, pull the dosing button out as far as it will go, until you see a **dark ring** on the pen. The dosing button should be easy to pull out without too much force being needed (figure 4).

**NOTE: Do not push the dosing button back in at this time. You will push it in when you are ready to self-inject the PegIntron.**


**Figure 5**

- Turn the dosing button until your prescribed dose is in line with the dosing tab. The button should turn easily without too much force being needed (figure 5). If you have trouble dialing your dose, check to make sure the dosing button has been pulled out **as far** as it will go.

**NOTE**: **If you cannot easily pull out the dosing button or dial the dose, do not use excessive force and do not use this pen because it may not deliver the correct dose.**

- Carefully lay the pen down on a hard, flat, non-slip surface. DO NOT remove either of the needle caps and DO NOT push the dosing button in until you are ready to self-inject the PegIntron dose.

**Step 4: Inject the PegIntron solution**

- Select the injection site. Your doctor will have told you which sites to use (e.g., thigh or abdomen). The best sites for giving yourself an injection are those areas with a layer of fat between the skin and muscle, like your thigh, the outer surface of your upper arm, and abdomen. Do not inject yourself in the area near your navel or waistline. If you are very thin, you should only use the thigh or outer surface of the arm for injection. **You should use a different site each time you inject PegIntron to avoid soreness at any one site.** Do not inject PegIntron into an area where the skin is irritated, red, bruised, infected, or has scars, stretch marks, or lumps.

- Clean the injection site skin with the second cleansing swab provided, and wait for the area to dry.

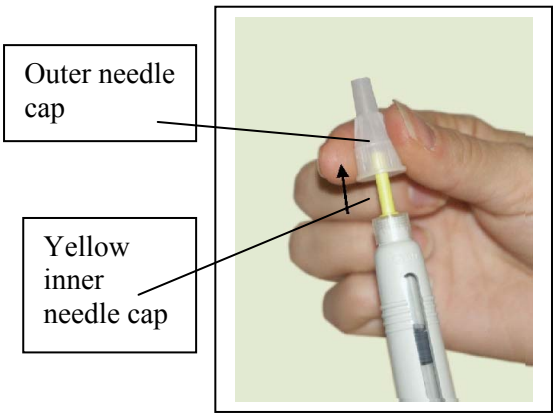


**Figure 6**

- Pull off the **outer needle cap (figure 6)**.
- There may be some liquid around the inner needle cap. Don't worry, this is normal. This liquid is not part of your dose, it is extra.
- Once the injection site is dry, pull off the **yellow inner needle cap** carefully exposing the injection needle. You are now ready to inject.

**Figure 7**

- **Hold the PegIntron pre-filled pen with your fingers wrapped around the pen body barrel and your thumb on the dosing button** (figure 7)**.**
- With your other hand, pinch a fold of loose skin in the area you have cleaned for injection.
- Insert the needle into the pinched skin at an angle of 45° to 90°.
- Press the dosing button down **slowly** and **firmly** until the button can no longer move.
- **Keep your thumb pressed down on the dosing button for an additional 5 seconds** to ensure that you get the complete dose.

- Remove the needle from your skin.
- Gently press the injection site with a small bandage or sterile gauze if necessary for a few seconds.
- Do not massage the injection site. If there is bleeding, cover with an adhesive bandage.
- Discard the PegIntron pre-filled pen with the needle safely in a closed rigid container.

**After 2 hours, check the injection site for redness, swelling, or tenderness.**
**If you have a skin reaction and it doesn't clear up in a few days, contact your health care professional.**